

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS  
ADVISORY COMMITTEE MEETING

Silver Spring, Maryland

Wednesday, January 23, 2008

2	<p>1 PARTICIPANTS:  2 Committee Members:  3 ALAN LEWIS BUCHMAN, M.D., Chair  Division of Gastroenterology  4 Northwestern University  5 LIN CHANG, M.D.  Center for Neurovisceral Sciences and Women's  6 Health  University of California, Los Angeles  7  8 MICHAEL S. EPSTEIN, M.D.  Anne Arundel Medical Center  9 KENNETH LOUIS KOCH, M.D.  Department of Internal Medicine  10 The Wake Forest University School of Medicine  11 GARY ROTH LICHTENSTEIN, M.D.  Gastroenterology Division  12 University of Pennsylvania  13 PANKAJ JAY PASRICHA, M.D.  Stanford University School of Medicine  14  SUZANNE ROSENTHAL Crohn's &amp; Colitis Foundation of  15 America  16 Temporary Voting Members:  17 JoELLEN CORKERY-DeLUCA  Patient Representative  18  19 JOSEPH J. CULLEN, M.D.  Division of Gastrointestinal, Minimally  Invasive &amp; Bariatric Surgery  20 Veterans Affairs Medical Center  21 SEAN P. HENNESSY  University of Pennsylvania School of Medicine  22</p>	4
3	<p>1 PARTICIPANTS (CONT'D):  2 Temporary Voting Members (Cont'd):  3 JUDITH M. KRAMER, M.D.  Duke University Medical Center  4  ALEXANDER H. KRIST, M.D.  5 Virginia Commonwealth University  6 ROBERT A. LEVINE, M.D.  State University of New York  7 Upstate Medical University, Syracuse  8 ABRAHAM MICHAEL LINCOFF, M.D.  Department of Cardiovascular Medicine  9 The Cleveland Clinic Foundation  10 MICHAEL A. PROSCHAN  Office of Biostatistics Research  11 National Institute of Allergy and Infectious  Diseases  12  13 RONALD RICHARDSON, M.D.  Department of Medical Oncology  Mayo Clinic  14  15 DOUGLAS R. ROSING, M.D.  Cardiology Consultation Service  National Institutes of Health  16  17 MARK A. TALAMINI, M.D.  Department of Surgery  UCSD Medical Center  18  19 Food and Drug Administration (Non-Voting):  20 JULIE G. BEITZ, M.D.  Office of Drug Evaluation  Center for Drug Evaluation and Research  21  22 TAMAL CHAKRABORTI  Division of Gastroenterology Products  Center for Drug Evaluation and Research</p>	5
2	<p>1 PARTICIPANTS (CONT'D):  2 Food and Drug Administration (Non-Voting)  3 MARJORIE DANNIS, M.D.  Division of Gastroenterology Products  4 Center for Drug Evaluation and Research  5 RUYI HE, M.D.  Division of Gastroenterology Products  6 Center for Drug Evaluation and Research  7 CLAUDIA KARWOSKI  Office of Surveillance and Epidemiology  8 Center for Drug Evaluation and Research  9 JOYCE A. KORVICK, M.D.  Division of Gastroenterology Products  10 Center for Drug Evaluation and Research  11 JOYCE WEAVER  Office of Surveillance and Epidemiology  12 Center for Drug Evaluation and Research  13 Designated Federal Official:  14 MIMI T. PHAN  Center for Drug Evaluation and Research  15  16 Other Attendees:  17  18 JOHN ALEXANDER, M.D.  Duke University  19 JOHN CAMM, M.D.  St. George's Hospital Medical School  20  21 SONIA CASTILLO CONOR DELANEY, M.D.  University Hospitals of Cleveland  22</p>	5

6	<p>1 PROCEEDINGS</p> <p>2 (8:00 a.m.)</p> <p>3 DR. BUCHMAN: Good morning, everyone.</p> <p>4 I'm going to call the meeting to order here.</p> <p>5 I'm Dr. Alan Buchman, professor of medicine and</p> <p>6 surgery at Northwestern University's Feinberg</p> <p>7 School of Medicine. And I'm going to introduce</p> <p>8 Mimi Phan, who's got some business statements to</p> <p>9 read.</p> <p>10 MS. PHAN: Good morning. Before we</p> <p>11 start the meeting, I just want to read some</p> <p>12 procedure for the public and the members who are</p> <p>13 here.</p> <p>14 For the topics such as those being</p> <p>15 discussed at today's meetings, there are</p> <p>16 often a variety of opinions, some of which</p> <p>17 are quite strongly held. Our goal is that</p> <p>18 today's meeting will be a fair and open forum</p> <p>19 for discussion of these issues, and that</p> <p>20 individuals can express their views without</p> <p>21 interruption. Thus, as a gentle reminder,</p> <p>22 individuals will be allowed to speak into the</p>	8
7	<p>1 record only if recognized by the chair.</p> <p>2 In the spirit of the Federal</p> <p>3 Advisory Committee Act and the Government in</p> <p>4 the Sunshine Act, we ask that the advisory</p> <p>5 committee members take care that their</p> <p>6 conversations about the topic today take</p> <p>7 place in the open forum of the meeting and</p> <p>8 not during lunch or breaks.</p> <p>9 We are also aware that members of</p> <p>10 the media are anxious to speak with the FDA</p> <p>11 about these proceedings. However, like the</p> <p>12 advisory committee members, FDA will refrain</p> <p>13 from discussing the details of this meeting</p> <p>14 with the media until its conclusion. For the</p> <p>15 convenience of media representatives I would</p> <p>16 like to identify the FDA press contact,</p> <p>17 Ms. Rita Chappelle. Are you in the audience?</p> <p>18 Please stand. To your left.</p> <p>19 And finally, I would like to remind</p> <p>20 everyone present to please silence your cell</p> <p>21 phone or pager if you have not already done</p> <p>22 so. We look forward to an interesting and</p>	9
6	<p>1 productive meeting. Thank you for your</p> <p>2 participation and cooperation.</p> <p>3 DR. BUCHMAN: I'm going to open the</p> <p>4 meeting of the Gastrointestinal Drugs Committee</p> <p>5 to evaluate Entereg, alvimopan, for the</p> <p>6 acceleration of recovery time for upper and</p> <p>7 lower gastrointestinal recovery following</p> <p>8 partial large or small bowel resection surgery</p> <p>9 and primary anastomosis.</p> <p>10 Let's begin with a roll call. If</p> <p>11 the voting members of the committee could</p> <p>12 introduce themselves by name and institution</p> <p>13 or where you're from, and we'll start with</p> <p>14 Dr. Rosing and work our way around the table.</p> <p>15 Please press the red button on your</p> <p>16 microphone to speak.</p> <p>17 DR. ROSING: Douglas Rosing, the</p> <p>18 National Institutes of Health.</p> <p>19 DR. CULLEN: Joe Cullen, University of</p> <p>20 Iowa.</p> <p>21 DR. KRIST: Alex Krist, Virginia</p> <p>22 Commonwealth University.</p>	8
7	<p>1 MR. PROSCHAN: Mike Proschan, National</p> <p>2 Institute of Allergy and Infectious Diseases.</p> <p>3 DR. PASRICHA: Jay Pasricha, Stanford</p> <p>4 University.</p> <p>5 DR. LEVINE: Bob Levine, State</p> <p>6 University of New York, Upstate Medical</p> <p>7 University, Syracuse.</p> <p>8 MS. CORKERY-DeLUCA: JoEllen DeLuca,</p> <p>9 Spartanburg, South Carolina, your patient</p> <p>10 consultant.</p> <p>11 DR. RICHARDSON: Ron Richardson, Mayo</p> <p>12 Clinic, Rochester, Minnesota.</p> <p>13 DR. CHANG: Lin Chang, UCLA.</p> <p>14 DR. KRAMER: Judith Kramer, Duke</p> <p>15 University Medical Center.</p> <p>16 MS. PHAN: Mimi Phan, federal rep,</p> <p>17 designed federal official.</p> <p>18 MR. HENNESSY: Good morning. I'm Sean</p> <p>19 Hennessy. I do pharmacoepidemiology research at</p> <p>20 the University of Pennsylvania.</p> <p>21 DR. LINCOFF: Michael Lincoff from the</p> <p>22 Cleveland Clinic Foundation.</p>	9

10	<p>1 DR. TALAMINI: Mark Talamini, 2 University of California, San Diego. 3 MS. KARWOSKI: Claudia Karwoski, team 4 leader for risk management, Office of 5 Surveillance and Epidemiology at FDA. 6 MS. WEAVER: Joyce Weaver, Office of 7 Surveillance and Epidemiology, FDA. 8 DR. HE: Ruyi He, medical team leader, 9 Division of GI, FDA. 10 DR. KORVICK: Joyce Korvick, deputy 11 director, Division of Gastroenterology, FDA. 12 DR. BEITZ: Julie Beitz, office 13 director, CDER, FDA. 14 DR. BUCHMAN: Thank you. I'd like to 15 introduce Dr. Korvick, who's going to introduce 16 the speakers for our sponsors. But prior to 17 that, Ms. Phan is going to read a Conflict of 18 Interest Statement. 19 MS. PHAN: Good morning. This is the 20 Conflict of Interest Statement for the 21 Gastrointestinal Drugs Advisory Committee. 22 Today is January 23, 2008.</p>	12	<p>1 authorized FDA to grant waivers to special 2 government employees who have potential 3 financial conflicts when it is determined 4 that the agency's need for a particular 5 individual's services outweighs his or her 6 potential financial conflict of interest. 7 Under 712 of the FD&amp;C Act, Congress 8 has authorized FDA to grant waivers to 9 special government employees, or regular 10 government employees with potential financial 11 conflicts when necessary to afford the 12 committee essential expertise. 13 Related to the discussions of 14 today's meeting, members and consultants of 15 this committee who are special government 16 employees have been screened for potential 17 financial conflicts of interest of their own 18 as well as those imputed to them, including 19 those of their spouses or minor children, and 20 for purposes of 18 U.S.C. 208, their 21 employers. 22 These interests may include</p>
11	<p>1 The Food and Drug Administration is 2 convening today's meeting of the 3 Gastrointestinal Drugs Advisory Committee 4 under the authority of the Federal Advisory 5 Committee Act of 1972. With the exception of 6 the industry representative, all members and 7 consultants are special government employees 8 or regular federal employees from other 9 agencies, and are subject to federal conflict 10 of interest laws and regulations. 11 The following information on the 12 status of the committee's compliance with 13 federal ethics and conflict of interest laws 14 covered by, but not limited to, those found 15 at 18 U.S.C. 208 and 712 of the federal Food, 16 Drug, and Cosmetic Act is being provided to 17 participants in today's meeting and to the 18 public. FDA has determined that members and 19 consultants of this committee are in 20 compliance with federal ethics and conflict 21 of interest laws. 22 Under 18 U.S.C. 208, Congress has</p>	13	<p>1 investments, consulting, expert witness 2 testimony, contracts, grants, CRADAs, 3 teaching, speaking, writing, patents and 4 royalties, and primary employment. 5 Today's agenda involves discussion 6 of safety and efficacy of Entereg (alvimopan) 7 new drug application 21-775 by Adolor 8 Corporation for the proposed indication of 9 acceleration of time to upper and lower 10 gastrointestinal recovery following partial 11 large or small bowel resection surgery with 12 primary anastomosis. 13 Based on the agenda for today's 14 meeting and all financial interests reported 15 by the committee members and consultants, 16 conflict of interest waivers have been issued 17 in accordance with U.S.C. 208(b)(3) and 712 18 of the FD&amp;C Act for Drs. Epstein and 19 Hennessy. 20 Dr. Epstein has been granted this 21 waiver for his speaker bureau activity for a 22 competing firm on an unrelated issue.</p>

14	<p>1 Dr. Epstein received less than \$10,001 per 2 year.</p> <p>3 Dr. Hennessy has been granted this 4 waiver for his unrelated consulting to the 5 competing firm.</p> <p>6 Dr. Hennessy received less than 7 \$10,001 per year. In accordance with 18 8 U.S.C. 208(b)(1), a conflict of interest 9 waiver has been issued to Dr. Joseph Cullen. 10 Dr. Cullen has been granted this waiver for 11 his activities as a co-investigator on a 12 competing product. The study is funded for 13 less than \$100,000 per year.</p> <p>14 The waiver allows these individuals 15 to participate fully in today's 16 deliberations. FDA's reasons for issuing the 17 waivers are described in the waivers 18 document, which are posted on FDA's web site 19 at <a href="http://www.fda.gov/ohrms/dockets/default.htm">www.fda.gov/ohrms/dockets/default.htm</a>. 20 Copies of the waivers may be obtained by 21 submitting a written request to the agency's 22 Freedom of Information Office, Room 6-30 of</p>	16	<p>1 other participants to advise the committee of 2 any financial relationships that they may 3 have with any firms at issue.</p> <p>4 DR. BUCHMAN: Dr. Korvick is going to 5 introduce our first presenter from the sponsor. 6 Please note that all questions for the sponsor 7 are to be held until the end of the sponsor's 8 full presentations.</p> <p>9 Joyce?</p> <p>10 DR. KORVICK: Thank you, Dr. Buchman. 11 Welcome, members of the advisory committee. 12 Today, before we get started with the sponsor's 13 presentation, I'm going to give you a brief 14 introduction.</p> <p>15 As you said, we're here to talk 16 about the efficacy and safety of alvimopan, 17 or Entereg, for the proposed indication, 18 which is to accelerate the time to upper and 19 lower gastrointestinal recovery following 20 partial large or small bowel resection 21 surgery with primary anastomosis. 22 Currently, there are no drugs</p>
15	<p>1 the Parklawn Building. A copy of this 2 statement will be available for review at the 3 registration table during this meeting and 4 will be included as part of the official 5 transcript.</p> <p>6 FDA regrets that there is no 7 industry representative participating in 8 today's meeting. Four different industry 9 representatives were invited. However, none 10 could attend.</p> <p>11 In addition, FDA wants it noted for 12 the record that our consumer representative 13 cancelled her attendance yesterday due to a 14 critical illness in her family.</p> <p>15 We would like to remind members and 16 consultants that if the discussions involve 17 any other products or firms not already on 18 the agenda for which an FDA participant has a 19 personal or imputed financial interest, the 20 participants need to exclude themselves from 21 such involvement, and their exclusion will be 22 noted for the record. FDA encourages all</p>	17	<p>1 approved for this indication.</p> <p>2 As the sponsor proposes, this 3 product is not intended to be used as an 4 outpatient therapy for this indication. 5 Today, you will discuss the efficacy and 6 safety.</p> <p>7 First of all, there are five 8 studies submitted for the postoperative ileus 9 indication. And it's been described in your 10 background package that Adolor is the sponsor 11 that is developing that indication. It will 12 be of interest to FDA for you to have a 13 discussion regarding the primary evaluation 14 endpoint for this indication.</p> <p>15 As has been noted in your 16 background packages, this development program 17 evolved over time. In the course of 18 development in the five different studies, 19 there were different patient populations, so 20 these included total abdominal hysterectomy 21 patients as well as small and large bowel 22 surgery resections. And as well, the primary</p>

<p style="text-align: right;">18</p> <p>1 outcome variable was originally in some of  2 these designed GI-3. Currently, we focus on  3 GI-2, which we've agreed with the sponsor is  4 probably a very relevant endpoint.  5 There is also a secondary endpoint  6 called discharge order written and ready as  7 defined as the time from the end of surgery  8 to the time ready for hospital discharge,  9 based solely on the recovery of GI function  10 as determined by a surgeon. So for that part  11 of the advice that we're seeking from you,  12 we're interested in, you know, the usefulness  13 of these various indications, but we also  14 have to look at the specific primary outcome  15 variable and get your impression on the  16 efficacy with regard to how that worked out  17 in these studies.  18 And you will see, we have a list of  19 questions. And one that is very interesting  20 to us is what is the minimum time? That  21 would be clinically meaningful for a  22 statistically significant outcome.</p>	<p style="text-align: right;">20</p> <p>1 drug.  2 And finally, it will be important  3 then to put that in a sort of risk-benefit  4 equation. And we will take a vote on whether  5 you recommend approval or not. But prior to  6 that, we also want your input on the proposed  7 risk management plan and have some discussion  8 there as proposed by the sponsor.  9 So we look forward to a lively  10 day's discussion. And I will turn the  11 meeting back over the Dr. Buchman and the  12 Adolor company for them to resume their  13 presentation.  14 DR. BUCHMAN: Okay. Our first  15 presenter from the Adolor Corporation is Linda  16 Young, a registered pharmacist, who's vice  17 president of regulatory affairs, who's going to  18 give an introduction on Entereg capsules.  19 MS. YOUNG: Good morning. I am Linda  20 Young, vice president of regulatory affairs.  21 And welcome, Dr. Buchman, members of the FDA,  22 the committee, and guests. Thank you for being</p>
<p style="text-align: right;">19</p> <p>1 Then we move on to safety. For the  2 postoperative ileus indication and studies,  3 as you'll hear from the sponsor and Dr. He, I  4 think the safety was relatively  5 straightforward. However, during the  6 development of this product by GSK for the  7 longer-term opioid-induced constipation,  8 there were some adverse events that showed up  9 in those studies.  10 They're here today to present some  11 of that preliminary data. And you should  12 realize that those projects are still in  13 development, and that we are not here to  14 discuss the indication for opioid-induced  15 bowel dysfunction. But that information was  16 brought to you today to further illuminate  17 the safety profile of this drug. So  18 regarding safety, we're interested in the  19 committee's opinion regarding the short-term  20 use of alvimopan, and how any of these safety  21 information data that you hear will affect  22 your evaluation of the short-term use of the</p>	<p style="text-align: right;">21</p> <p>1 here today.  2 We are here today to discuss the  3 safety and efficacy of Entereg, a novel  4 compound in a new class for the management of  5 postoperative ileus and bowel resection.  6 Postoperative ileus, or POI, is a serious  7 condition, with an adverse impact on both the  8 patient and the health care system.  9 There is a recognized morbidity  10 associated with POI, one of the most common  11 causes of delayed hospital discharge.  12 Currently, there is an unmet need in POI, as  13 there is no FDA-approved agent for this  14 condition. But as the data will show,  15 Entereg provides for the effective management  16 of POI following bowel resection.  17 Entereg is the trademarked name for  18 alvimopan, a selective, peripherally acting,  19 mu-opioid receptor antagonist. Entereg  20 mitigates the adverse effects of opioids on  21 the GI motility without blocking their  22 beneficial analgesic effects.</p>

22	<p>1 In patients undergoing bowel 2 resection, this results in earlier resolution 3 of GI recovery and earlier hospital 4 discharge.</p> <p>5 Adolor has been developing Entereg 6 since 1999, and we've collaborated with the 7 FDA throughout the development process. Over 8 the years, several indications have been 9 studied with Entereg, but since 2000, Adolor 10 has focused on postoperative ileus and acute 11 care indication in an inpatient setting.</p> <p>12 GlaxoSmithKline is working toward 13 an indication for chronic care opioid bowel 14 dysfunction, or OBD, in outpatient setting. 15 Because we are only seeking the postoperative 16 ileus indication today, we will focus our 17 discussion mainly on the safety and efficacy 18 of Entereg for POI.</p> <p>19 We filed the NDA for Entereg in 20 2004. It included Phase III study data from 21 mixed populations of largely bowel 22 resections, but also total abdominal</p>	24	<p>1 a robust data set from a study of bowel 2 resection patients using the 12-milligram 3 dose. During the review of Study 314, we 4 received interim data from Study GSK014, a 5 12-month safety trial, not in POI, but in the 6 OBD patients on chronic opioid therapy. 7 These data led the FDA to issue another 8 approvable letter, asking for final data from 9 GSK014 and a risk management plan. 10 Therefore, as requested by the agency, we 11 will also briefly address these safety 12 findings from the study. And all of this 13 brings us to today's meeting.</p> <p>14 Adolor believes that robust safety 15 and efficacy data that will be presented 16 today provides compelling evidence to support 17 approval of Entereg for POI following bowel 18 resection. When used in this acute care 19 setting, there is a favorable benefit-risk 20 ratio, permitting this product to enter the 21 market to fulfill the unmet need and to 22 provide a clinically meaningful benefit to</p>
23	<p>1 hysterectomy patients, with the doses of both 2 6 and 12 milligrams. We saw variability in 3 responses in the combined population, but 4 there was a consistent response in the bowel 5 resection subgroup and especially at the 6 12-milligram dose. We agreed with the agency 7 to focus future studies on bowel resection, 8 the subgroup that did well, and we also 9 proposed the 12-milligram dose because it 10 gave the most consistent response, and the 11 safety profile was similar to 6 milligrams.</p> <p>12 During the NDA review, GSK was 13 conducting a POI study in Europe: Study 001. 14 In this study Entereg did not show clinical 15 superiority to placebo. But we learned that 16 in Europe, clinical practice and 17 socioeconomic systems are different. This 18 point will be further explained by my 19 colleague, Dr. Techner.</p> <p>20 Given these data, the agency issued 21 an approvable letter and asked for further 22 efficacy data. We then submitted Study 314,</p>	25	<p>1 patients.</p> <p>2 Adolor has also shown its 3 commitment to the safe use of this product 4 through the development of a risk management 5 plan, which Dr. Jackson will review later in 6 our presentation.</p> <p>7 We are fortunate to have with us 8 today several experts who will help us 9 demonstrate the medical need and the clinical 10 benefits of Entereg and POI. Dr. Senagore 11 will share a surgical perspective of POI. 12 Dr. Lee Techner will outline the POI 13 development program and present the efficacy 14 data. Dr. Jackson will present the safety 15 data from our clinical trials.</p> <p>16 And Dr. Eric Mortensen from 17 GlaxoSmithKline will discuss the safety 18 findings from the OBD study, GSK014.</p> <p>19 Dr. Jackson will then conclude with 20 a summary of our findings and an overview of 21 our proposed risk management plan.</p> <p>22 In addition, we are joined today by</p>

26	<p>1 the following experts who will be available  2 to answer your questions: John Alexander,  3 cardiologist, Duke University; John Camm,  4 cardiologist, St. George's Hospital Medical  5 School; Conor Delaney, surgeon, University  6 Hospitals of Cleveland; Charles Fuchs,  7 oncologist, Dana-Farber Cancer Institute;  8 Gary Koch, statistician, University of North  9 Carolina; and Kenneth Lyles, endocrinologist,  10 Duke University.</p> <p>11 I now would like to invite  12 Dr. Senagore to the podium.</p> <p>13 DR. SENAGORE: Thank you, Linda,  14 Dr. Buchman, members, and guests. My name is  15 Anthony Senagore, and I'm a professor of surgery  16 at Michigan State University College of Human  17 Medicine, and vice president of research and  18 education at Spectrum Health in Grand Rapids,  19 Michigan. I've been asked to give a surgical  20 perspective on the condition of postoperative  21 ileus.</p> <p>22 Postoperative ileus and bowel</p>	28	<p>1 only impairs the patient's recovery.</p> <p>2 Postoperative ileus is  3 traditionally associated with several  4 clinical signs, including the presence of  5 nausea and vomiting, the absence of passage  6 of flatus or stool, abdominal bloating,  7 distension of the abdomen, and in turn,  8 abdominal pain and discomfort.</p> <p>9 Over the last decade, we have  10 gained considerable knowledge regarding the  11 etiology of ileus. One of the components of  12 developing ileus is the surgical stress  13 response. This happens after major surgical  14 intervention, and is a complex interplay of  15 biological factors, including neurogenic  16 factors related to the autonomic nervous  17 system, and a variety of hormones and  18 neuropeptides which are released in direct  19 response to the stress.</p> <p>20 There is also increasing knowledge  21 showing that a variety of inflammatory  22 mediators contribute to the development of</p>
27	<p>1 resection is a significant problem. There  2 are about 400,000 bowel resections performed  3 annually in the U.S. It is estimated that  4 90 percent of these cases are still performed  5 by open surgical technique. Postoperative  6 ileus occurs in all of these patients.</p> <p>7 Postop ileus is the most common  8 cause of prolonged hospital stay after bowel  9 resection, frequently leading to additional  10 interventions. And surgeons cannot predict  11 which of these patients will go on to develop  12 a more severe form of POI.</p> <p>13 POI is defined as the transient  14 cessation of coordinated bowel motility after  15 surgery, preventing effective transit of  16 intestinal contents and/or tolerance of oral  17 intake. When I trained as a surgeon, we were  18 taught that POI was a protective response to  19 surgery, that it rested the anastomosis, and  20 improved healing. Today, we know better.  21 POI offers no physiologic benefit or  22 advantage for an anastomotic healing, and</p>	29	<p>1 postoperative ileus. Surgical anesthetics  2 may also be involved. Both inhalational  3 gases and intravenous agents may impair GI  4 motility, and they tend to have a primary  5 effect on the colon.</p> <p>6 The most significant identified  7 factor, however, is the role of opioid  8 analgesics, particularly with parenteral  9 administration. Opioids are known to bind to  10 the mu-opioid receptors with the enteric  11 nervous system. They block the excitatory  12 neurons, which innervate intestinal smooth  13 muscle, and thereby inhibit both  14 gastrointestinal motility and secretion.</p> <p>15 But from the patient's perspective,  16 opioid-based patient-controlled analgesia has  17 become the standard of care for the  18 management of postoperative pain,  19 particularly after bowel resection.  20 Opioid-based PCA pumps have been shown to  21 provide more effective analgesia, shorten  22 hospital stay, and improve overall patient</p>

30	<p>1 satisfaction. Despite these benefits, PCAs 2 are associated with a higher incidence of 3 documented postoperative ileus on hospital 4 coding.</p> <p>5 So in an ideal world, when should a 6 patient recover after abdominal surgery? A 7 recent consensus conference data suggests 8 that an optimum time to recovery would be 9 within five days of surgery, after which we 10 would diagnose prolonged or serious POI. 11 Unresolved ileus is associated with an 12 extended hospital stay as well as with a 13 variety of associated morbidities, including 14 nosocomial infections and pulmonary 15 complications.</p> <p>16 Furthermore, management of 17 prolonged POI and associated complications 18 frequently results in additional medical and 19 surgical interventions. For this reason, the 20 primary clinical objective following bowel 21 resection is the avoidance of POI. Thus, in 22 studies relating to enhanced recovery</p>	32	<p>1 complications, such as intravenous catheter 2 infection, urinary tract infection, and 3 pulmonary compromise.</p> <p>4 The costs associated with severe 5 POI are substantial. When we examine large 6 administrative data sets, we see two distinct 7 patient populations: Those where surgeons 8 have documented the development of POI and 9 hospital coders have captured that data for 10 bill submission; and those that are uncoded, 11 and therefore, were not felt by the 12 caregivers to have POI. Looking at length of 13 stay, patients with coded POI have nearly a 14 week's longer length of stay. And that 15 prolonged hospitalization translates into a 16 nearly doubling of hospital costs.</p> <p>17 Further examination of these data 18 reveal that these patients also have a 19 significantly higher in-hospital mortality 20 rate.</p> <p>21 Current treatment options for POI 22 focus on the use of multimodal accelerated</p>
31	<p>1 pathways after major abdominal surgery, the 2 time to recovery of bowel function has been 3 the primary clinical endpoint.</p> <p>4 Patients with POI suffer discomfort 5 from nausea, vomiting, abdominal distension, 6 and NG tube insertion, which can cause 7 complications such as pneumonia and 8 atelectasis.</p> <p>9 As I mentioned previously, POI is 10 the most common cause for prolonged hospital 11 stay after bowel resection. The POI patient 12 consumes significantly greater hospital and 13 nursing resources. There's a need to manage 14 the NG tube, monitor fluid balance, and 15 assess vital signs more frequently. This 16 support often will progress to the 17 administration of TPN for nutritional support 18 and further monitoring and data collection.</p> <p>19 Prolonged hospitalization adversely 20 affects patient census and hospital 21 throughput. And it is directly correlated 22 with the risk of the so-called preventable</p>	33	<p>1 postoperative care pathways, which frequently 2 require intense nursing and physician input 3 and coordination. These pathways involve 4 early removal of the nasogastric tube, early 5 acceleration of dietary advancement, and an 6 emphasis on early ambulation of the patient. 7 Opioid-sparing analgesia is sometimes used to 8 minimize the deleterious effects of opioids.</p> <p>9 Prokinetics have also been studied. 10 However, none are approved or routinely 11 available in preventing or treatment 12 postoperative ileus. In fact, none of these 13 approaches have consistently shortened 14 hospital stay in large population studies.</p> <p>15 From a clinical perspective, a 16 commonly used metric for evaluating the 17 treatment strategy is NNT, or number needed 18 to treat. How can we compare the NNT of 19 alvimopan for POI prophylaxis with two 20 commonly recommended and currently 21 CMS-mandated prophylactic measures for other 22 surgical patients?</p>

<p style="text-align: right;">34</p> <p>1 A large meta-analysis of  2 prophylactic measures for DBT and surgical  3 site infection in colorectal cancer patients  4 revealed an NNT that ranged from 4 to 17. In  5 comparison, as you will hear shortly by  6 Dr. Techner, the NNT for alvimopan for POI  7 prophylaxis, using discharge order within  8 seven days as the outcome measure, is five to  9 nine, clearly within this same range.  10 Thus, we are left with no approved  11 drugs for the prevention or management of  12 postoperative ileus, and the current  13 management options are limited and not  14 consistently effective. We have no reliable  15 criteria to predict who will develop either a  16 prolonged or severe postoperative ileus, and  17 the burden on the patient and the health care  18 system is severe. So as clinicians, we feel  19 that postoperative ileus should be managed  20 proactively in bowel resection patients with  21 an agent that should decrease the  22 manifestations of this condition.</p>	<p style="text-align: right;">36</p> <p>1 focus on alvimopan's mechanism of action and  2 rationale for its use in the management of  3 postoperative ileus.  4 Alvimopan is a highly selective,  5 competitive antagonist at the mu-opioid  6 receptor. It is metabolized to an active  7 metabolite by gut microflora. The metabolite  8 is equipotent to alvimopan, but is not  9 required for efficacy in POI.  10 Alvimopan and its metabolite are  11 peripherally acting, and much less potent at  12 both delta and kappa receptors. Furthermore,  13 alvimopan demonstrated no activity at any of  14 over 70 non-opioid receptors, enzymes, and  15 ion channels, thus reducing the potential for  16 off-target effects.  17 Alvimopan competes with opioid  18 analgesics such as morphine or fentanyl for  19 binding it in the opioid receptors located  20 within the enteric nervous system. In fact,  21 alvimopan's affinity for the mu receptor is  22 over 40-fold greater than that of morphine.</p>
<p style="text-align: right;">35</p> <p>1 I'd like to ask Dr. Techner now to  2 discuss Adolor's clinical development and POI  3 efficacy results.  4 DR. TECHNER: Good morning. I'm Lee  5 Techner, senior medical director for Adolor.  6 Today, it is my privilege to share with you the  7 efficacy results from the Phase III clinical  8 trials supporting the use of alvimopan,  9 12 milligrams, for the management of  10 postoperative ileus following segmental bowel  11 resection. I'll start by providing a brief  12 overview of alvimopan's mechanism of action,  13 then review study design endpoints and the  14 efficacy results. I'll conclude the  15 presentation with a brief summary.  16 An extensive clinical pharmacology  17 program has been completed, characterizing  18 the mechanism of action, pharmacologic  19 efficacy, pharmacokinetic profile, and  20 exposure response of alvimopan. An overview  21 of the findings has been provided in your  22 briefing document. This morning, I will</p>	<p style="text-align: right;">37</p> <p>1 Once bound, alvimopan blocks the negative  2 effects of opioids on bowel motility without  3 compromising central analgesia.  4 As you've heard this morning,  5 opioid analgesics are a key factor in the  6 development and duration of postoperative  7 ileus. Therefore, the use of a peripherally  8 acting mu-opioid receptor antagonist directly  9 targets a primary component of this serious  10 surgical condition.  11 Now let's turn our attention to the  12 alvimopan Phase III POI clinical development  13 program. Overall study design was similar  14 across all Phase III trials. Initially, we  15 evaluated both 6- and 12-milligram doses.  16 Patients received their first dose of  17 alvimopan or placebo preoperatively in order  18 to mitigate the GI effects of highly potent  19 opioids commonly administered during  20 induction of anesthesia.  21 Dosing continued postoperatively  22 until discharge, or for a maximum of seven</p>

38	<p>1 days, if the patient remained in the 2 hospital.</p> <p>3 Adverse events were assessed up to 4 Day 14. Active monitoring of sites for 5 serious adverse events continued for 30 days 6 following the last dose of study drug, or 7 until resolution. Patients typically 8 returned to their surgeon for the initial 9 postoperative evaluation within two to four 10 weeks of discharge, corresponding to the 11 adverse event monitoring period.</p> <p>12 Four alvimopan doses were evaluated 13 in Phase II dose-ranging studies, of which 14 two were chosen for the initial Phase III 15 trials: 6 and 12 milligrams. Of these, the 16 12-milligram dose appears to be optimal for 17 the bowel resection population when examined 18 from several perspectives.</p> <p>19 Population PK analysis demonstrate 20 that with BID dosing plasma concentrations 21 remained above the KI for the mu-opioid 22 receptor for 12 hours in 95 percent of</p>	40	<p>1 advancement, with liquids offered on 2 Postoperative Day 1 and solids on Day 2.</p> <p>3 Key inclusion criteria required 4 that patients over 18 years had an ASA score 5 of I to III and were scheduled for partial 6 large or small bowel resection with primary 7 anastomosis or total abdominal hysterectomy, 8 all performed by laparotomy. In addition, 9 patients were required to receive 10 opioid-based IV patient-controlled analgesia 11 for postoperative pain management. The 12 opioid used was at the discretion of the 13 investigator.</p> <p>14 Patients were excluded from the 15 trials if they were scheduled for total 16 colectomy, colostomy, ileostomy, or had a 17 complete bowel obstruction, used opioids 18 chronically, or received more than three 19 doses of opioid analgesics within seven days 20 prior to surgery.</p> <p>21 In the POI development program, 22 three measures were evaluated to support</p>
39	<p>1 patients receiving the 12-milligram dose, two 2 times longer than that achieved with 3 6 milligrams.</p> <p>4 Clinical trial results demonstrated 5 a consistent and robust treatment effect with 6 alvimopan 12 milligrams, particularly in the 7 North American trials enrolling the largest 8 number of bowel resection patients, which I 9 will discuss shortly. And the safety 10 profiles of both the 6- and 12-milligram 11 doses are comparable. Therefore, consistent 12 with the proposed label, efficacy results 13 will be presented for the 12-milligram dose 14 only.</p> <p>15 A standardized accelerated 16 multimodal postoperative care pathway was 17 implemented in all trials in order to be 18 consistent with current best practices. This 19 consisted of early removal of the nasogastric 20 tube -- that is, no later than Postoperative 21 Day 1, early ambulation initiated on 22 Postoperative Day 1, and early diet</p>	41	<p>1 clinically meaningful benefit. GI recovery, 2 the primary measure of clinical progress 3 following major abdominal surgery, and the 4 main driver for discharge.</p> <p>5 Hospital length of stay. As we've 6 heard from Dr. Senagore, reduction in length 7 of stay is associated with substantial 8 benefits to both the patient and the health 9 care system.</p> <p>10 Insertion of a nasogastric tube for 11 symptoms of POI increases patient risk for 12 associated complications, some of which may 13 lead to serious morbidity or mortality. 14 Therefore, the incidence of postoperative NG 15 tube insertion was assessed in order to 16 determine whether alvimopan, through 17 accelerating GI recovery, could reduce the 18 need for this intervention.</p> <p>19 Upper and lower GI recovery are 20 required for complete resolution of POI. For 21 the initial alvimopan clinical trials, the 22 primary endpoint was a three-component</p>

42	<p>1 composite: GI-3, the last to occur of upper 2 GI recovery, represented by the time to 3 tolerating solid food, and lower GI recovery, 4 the first to occur of either flatus or bowel 5 movement.</p> <p>6 Resumption of colonic motility is 7 generally considered the rate-limiting factor 8 for complete resolution of POI. Clinically, 9 passage of stool is more closely associated 10 with this event when compared with flatus. 11 Therefore, for assessment of alvimopan's 12 treatment effect on GI recovery in bowel 13 resection patients, a two-component composite 14 endpoint is more clinically relevant. This 15 is represented by GI-2, the last to occur of 16 the time to tolerating solid food and the 17 time to first bowel movement.</p> <p>18 In agreement with FDA, GI-2 was the 19 primary endpoint in the most recent trial, 20 Study 314. GI-2 was a pre-specified 21 secondary endpoint in two of the North 22 American studies, 313 and 308; the non-U.S.</p>	44	<p>1 recovery. Today, we'll present our results 2 using an expanded responder definition 3 developed in collaboration with FDA and 4 surgeons for the most recent trial, 5 Study 314, and retrospectively applied to the 6 other North American studies. A responder is 7 defined as a patient that achieves the 8 endpoint of interest on any of Postsurgical 9 Days 3 through 8 and has no subsequent 10 adverse event reports of POI, which, 11 according to the investigator, either delayed 12 discharge or resulted in hospital readmission 13 within seven days of discharge.</p> <p>14 GI recovery by Day 5 and early 15 discharge are primary clinical objectives 16 following bowel resection. Therefore, using 17 our responder definition, we evaluated 18 whether treatment with alvimopan would allow 19 more patients to achieve these important 20 clinical milestones, thus potentially 21 reducing patient risk.</p> <p>22 In keeping with the proposed label</p>
43	<p>1 Study 001; and a post hoc analysis in 2 Study 302.</p> <p>3 The length of hospital stay was 4 characterized using several measures: ready 5 for discharge based solely on the time of GI 6 recovery as defined by the surgeon; time to 7 discharge order written, DOW, preferred over 8 actual time to hospital departure, as it 9 avoids the potential influence of confounding 10 factors such as social or transportation 11 issues; and finally, an approach more 12 consistent with how this measure is typically 13 reported, discharge order written by 14 postoperative day, referred to as "length of 15 stay." This measure uses the calendar day 16 the order was written as opposed to its 17 occurrence relative to the end of surgery 18 time.</p> <p>19 Because there is no precedent 20 defining a responder in POI, several analyses 21 were explored in the earlier trials, all 22 based on a single component: time to GI</p>	45	<p>1 indication, the efficacy results will focus 2 only on patients who underwent partial small 3 or large bowel resection with primary 4 anastomosis. Study 314, which enrolled only 5 bowel resection patients, Study 313 in which 6 93 percent of the patients enrolled underwent 7 bowel resection, will provide the primary 8 confirmation of clinical benefit.</p> <p>9 Studies 302 and 308, although not 10 designed to evaluate the bowel resection 11 population independently, provide additional 12 support for alvimopan's benefit in these 13 surgical patients.</p> <p>14 Study 306 was a safety study 15 enrolling only hysterectomy patients, and 16 unlike the other trials, had an outpatient 17 component. Therefore, this study will not be 18 included in discussion of the POI efficacy 19 results. The POI safety presentation, 20 however, will include data from all patients 21 who had surgery.</p> <p>22 Study 001 was the only non-U.S.</p>

46	<p>1 study, and differed from the North American 2 trials with respect to opioid use and length 3 of stay. Therefore, I will discuss results 4 from this trial first and then focus the 5 remainder of the presentation on the North 6 American studies.</p> <p>7 The prospectively defined analysis 8 population used to evaluate efficacy outcomes 9 was the modified intent-to-treat population, 10 defined as all patients who had at least one 11 dose of study drug, surgery as per protocol, 12 and at least one post-surgery efficacy 13 assessment. Ninety-four percent of bowel 14 resection patients in the North American 15 trials were included in the MITT bowel 16 resection population.</p> <p>17 The pre-specified primary approach 18 to evaluating alvimopan's treatment effect 19 was the Cox proportional hazards model, using 20 the P value associated with the resulting 21 hazard ratio. To describe the magnitude of 22 treatment effect, estimates of the mean time</p>	48	<p>1 elements of the Phase III POI clinical 2 development program, let's turn our attention 3 to the efficacy results, starting with the 4 non-U.S. Study 001.</p> <p>5 Study 001 was conducted outside 6 North America. Results for the bowel 7 resection population were not statistically 8 significant for the primary endpoint, GI-3. 9 Post hoc analyses provided additional 10 perspective, allowing a better understanding 11 of this outcome. Results of these analyses 12 highlighted significant differences between 13 Study 001 and the North American trials, 14 primarily with respect to opioid use and 15 length of stay.</p> <p>16 In the North American trials, use 17 of opioid-based IV PCA and restricted use of 18 non-opioid analgesics was mandated. This was 19 not the case in Study 001, which led to 20 greater than 60 percent higher use of 21 non-opioid analgesics, and 55 percent lower 22 utilization of opioid-based IV PCA. Overall</p>
47	<p>1 as well as the median and 75th percentile 2 time will be presented, and are derived from 3 the Kaplan-Meier curves as pre-specified in 4 the analysis plan. The FDA briefing document 5 provides median and 75th percentile estimates 6 derived from the Cox proportional hazards 7 model. In most cases, the results based on 8 either method are comparable.</p> <p>9 The difference in the mean times 10 was obtained from the area between the two 11 treatment group curves. As such, this area 12 may be viewed as the sum of differences 13 between the curves over the entire 10-day 14 observation period, or alternatively, across 15 the various percentiles. Differences in the 16 median and the 75th percentile supplement 17 information provided by the mean. Additional 18 measures further characterizing clinical 19 benefit include a responder analysis, which I 20 described earlier, and numbers needed to 21 treat, or NNT.</p> <p>22 Now that we've reviewed the key</p>	49	<p>1 postoperative opioid exposure was two times 2 higher in the North American trials.</p> <p>3 With respect to length of stay, we 4 learned that GI recovery was not a primary 5 determinant of discharge in Study 001. In 6 fact, the average time from GI recovery to 7 discharge order written, along with the 8 average hospital stay, were approximately 9 three days longer in the 001 placebo group as 10 compared with placebo patients in the North 11 American studies. This may be related to 12 regional variation and practice patterns, 13 along with other cultural differences that 14 impact decisions on discharge.</p> <p>15 Due to these differences, 16 meaningful interpretation of 17 discharge-related endpoints within the 18 context of the North American trials is 19 confounded and will not be presented. 20 However, the results are in your briefing 21 document.</p> <p>22 The mean age for the bowel</p>

<p style="text-align: right;">50</p> <p>1 resection population in Study 001 was  2 approximately 64 years, which is consistent  3 with the primary reason for surgery:  4 Colorectal cancer. Approximately 80 percent  5 of the patients completed treatment, and  6 there was a low discontinuation rate for  7 adverse events.</p> <p>8 For the bowel resection population  9 in Study 001, statistical significance was  10 not achieved for the primary endpoint GI-3.  11 For GI-2, the hazard ratio was 1.3, and  12 statistically significant when compared with  13 placebo. Mean and median differences between  14 treatment groups for GI recovery ranged from  15 3 to 11 hours, and 4 to 20 hours at the 75th  16 percentile, all favoring alvimopan.</p> <p>17 We will now focus on the results  18 from the North American studies. Over 2,200  19 patients were included in the North American  20 trials. Eighty-two percent underwent bowel  21 resection. As mentioned previously, the  22 highest proportion of bowel resection</p>	<p style="text-align: right;">52</p> <p>1 a higher proportion performed on the left  2 versus the right colon. Surgery duration was  3 similar across treatment groups and within  4 the expected range for these procedures. The  5 most common reasons for surgery was colon or  6 rectal cancer, followed by diverticular  7 disease, consistent with the frequency of GI  8 conditions requiring elective bowel resection  9 in the general population.</p> <p>10 These Kaplan-Meier curves represent  11 the pattern of GI recovery in bowel resection  12 patients based on integrated data from the  13 four North American trials. No events, bowel  14 movement or toleration of solids, are  15 occurring within the initial 48 hours  16 following surgery. At that point, the curves  17 separate, and they remain separated  18 throughout the entire postoperative  19 observation period of 10 days.</p> <p>20 The orange line, alvimopan  21 12 milligrams, remains to the left of the  22 gray placebo line at all time points. This</p>
<p style="text-align: right;">51</p> <p>1 patients were enrolled in Studies 314 and  2 313, 100 percent and 93 percent,  3 respectively.</p> <p>4 The proportion of patients  5 completing was slightly higher in the  6 alvimopan 12-milligram group compared with  7 placebo across all trials, with the exception  8 of Study 302. Adverse events were the most  9 common reason for discontinuations and higher  10 in placebo, primarily due to a numerically  11 higher incidence of nausea, vomiting, and  12 postoperative ileus as compared with  13 alvimopan-treated patients, again, with the  14 exception of Study 302.</p> <p>15 Patient demographics were  16 well-matched across treatment groups. Forty  17 percent of bowel resection patients were 65  18 years or older, and 17 percent greater than  19 or equal to 75 years or age, populations at  20 higher risk for perioperative complications.  21 Over 90 percent of resections were large  22 bowel, and consistent with clinical practice,</p>	<p style="text-align: right;">53</p> <p>1 shifting of the curve indicates that patients  2 treated with alvimopan had a higher  3 probability of earlier GI recovery from  4 Postoperative Day 2 through Day 10 as  5 compared with placebo. Between Postoperative  6 Days 5 and 6, representing patients with more  7 prolonged ileus and potentially at higher  8 risk for complications, the curves are at  9 their widest divergence.</p> <p>10 The mean difference in GI-2  11 recovery between alvimopan and placebo over  12 the 10-day observation period is 18.8 hours,  13 the difference at the median 10 hours, and a  14 22.4-hour difference at the 75th percentile.  15 These findings are supported by results from  16 the individual studies.</p> <p>17 In studies with the highest  18 proportion of bowel resection patients, 314  19 and 313, hazard ratios in the alvimopan  20 treatment group for both GI-2 and GI-3 were  21 greater than 1.4, and statistically  22 significant when compared with placebo.</p>

<p style="text-align: right;">54</p> <p>1 Further support is provided by Studies 308 2 and 302, where hazard ratios for GI-2 were 3 also statistically significant. A positive 4 trend was observed for the GI-3 endpoint in 5 these studies. However, statistical 6 significance was not achieved. 7       In Studies 314 and 313, 8 statistically significant results as measured 9 by the hazard ratios were associated with a 10 mean difference of 20 to 26 hours between the 11 treatment groups for GI-2 recovery. The 12 difference at the median, 17 hours. And at 13 the 75th percentile, GI recovery occurred up 14 to approximately 1-1/2 days earlier with 15 alvimopan as compared to placebo. These data 16 are supported by the other studies as well. 17 Although somewhat less robust, similar trends 18 were observed for GI-3. 19       The treatment effect of alvimopan 20 12 milligrams was consistent regardless of 21 sex, age, or race, with hazard ratios and 22 associated confidence intervals all above 1.</p>	<p style="text-align: right;">56</p> <p>1 and 313, with mean differences from placebo 2 ranging from 13 to 21 hours, and with similar 3 results seen in supportive studies. Across 4 all studies, differences from placebo at the 5 75th percentile were robust, ranging from 6 approximately 1 to 2 days. 7       The pattern of discharge order 8 written in the four North American studies is 9 represented by these Kaplan-Meier curves. 10 The repeating steps occur approximately every 11 12 hours, corresponding to clinical practice 12 patterns, with these orders typically written 13 during the first two nursing shifts. 14       In the North American trials, 15 approximately 90 percent of the discharge 16 orders were written between 7:00 a.m. and 17 7:00 p.m. The mean difference in DOW is 18 18 hours, the difference at the median 15.6 19 hours, and a 27-hour difference at the 75th 20 percentile. 21       In Studies 314 and 313, hazard 22 ratios for DOW were greater than or equal to</p>
<p style="text-align: right;">55</p> <p>1 Across all studies, a higher proportion of 2 patients receiving alvimopan achieved GI 3 recovery by Postsurgical Day 5, ranging from 4 10 to 18 percent greater than placebo-treated 5 patients. 6       When converted to NNTs, 5 to 10 7 patients would require treatment with 8 alvimopan to move one patient into this 9 earlier GI recovery period. 10       Resolution of POI is the driver for 11 discharge following bowel resection. 12 Therefore, achieving this clinical milestone 13 early may reduce overall hospital length of 14 stay. In patients receiving alvimopan, 15 hazard ratios for ready were 1.4 and 1.5 in 16 Studies 314 and 313, both statistically 17 significant when compared with placebo. 18 Similar results were demonstrated in 19 Studies 302 and 308. 20       The magnitude of treatment effect 21 by all measures was comparable to that 22 observed for GI recovery in both Studies 314</p>	<p style="text-align: right;">57</p> <p>1 1.4, and statistically significant when 2 compared with placebo. Similar findings were 3 demonstrated in Study 308. A positive trend 4 favoring alvimopan was observed in Study 302. 5 However, this was not statistically 6 significant. 7       Mean differences from placebo range 8 from to 19 hours in Studies 314 and 313, and 9 were comparable in Study 308. Differences at 10 the median range from 6 to 22 hours and 21 to 11 approximately 45 hours at the 75th percentile 12 across all studies. 13       A higher proportion of patients in 14 the alvimopan treatment group had discharge 15 orders written prior to Postsurgical Day 7 as 16 compared to placebo-treated patients, 12 to 17 approximately 15 percent in Studies 314 and 18 313, and similar findings in Studies 302 and 19 308. These differences correspond to NNTs 20 ranging from 5 to 9. When calculated using 21 the calendar day the discharge order was 22 written, mean postoperative length of stay</p>

<p style="text-align: right;">58</p> <p>1 was shortened by 1 day in Studies 314 and  2 313, with a comparable reduction in  3 Study 308.  4 Integrated results from the four  5 North American studies demonstrate hazard  6 ratios and associated confidence intervals  7 above 1 for primary and secondary endpoints.  8 Intervention to relieve symptoms  9 associated with unresolving postoperative  10 ileus often involves insertion of a  11 nasogastric tube. This can be associated  12 with serious complications, and does not  13 shorten the duration of POI. Treatment with  14 alvimopan 12 milligrams was associated with a  15 significant reduction in the incidence of  16 postoperative NG tube insertion as compared  17 with placebo. The difference of  18 approximately 5 percent corresponds to an NNT  19 of 20.  20 Effective pain management following  21 bowel resection is frequently achieved with  22 opioid-based IV PCA. Therefore, the</p>	<p style="text-align: right;">60</p> <p>1 the other North American trials, and achieved  2 even with implementation of a standardized  3 accelerated care pathway.  4 In the four North American trials  5 combined, treatment with alvimopan reduced  6 the incidence of postoperative NG tube  7 insertion by 43 percent. Across all studies,  8 treatment with alvimopan 12 milligrams had no  9 impact on pain management. We believe that  10 these results demonstrate clinically  11 meaningful benefit to patients undergoing  12 bowel resection.  13 I would now like to ask my  14 colleague, Dr. David Jackson, to lead the  15 presentation on the safety profile of  16 alvimopan.  17 DR. JACKSON: Thank you and good  18 morning. I'm David Jackson, the chief medical  19 officer for Adolor. And this morning, I would  20 like to present to you the POI safety data.  21 Before we do, I'm going to go and sit down again  22 and invite Dr. Mortensen from GSK to address the</p>
<p style="text-align: right;">59</p> <p>1 potential for alvimopan to compromise  2 analgesia was assessed. In the North  3 American clinical trials, treatment with  4 alvimopan had no impact on either opioid  5 consumption or VAS pain scores. This finding  6 has been consistent across all studies.  7 In summary, treatment with  8 alvimopan 12 milligrams in the studies where  9 greater than 90 percent of patients enrolled  10 underwent bowel resection resulted in  11 statistically significant acceleration of GI  12 recovery and an associated reduction in  13 hospital length of stay; mean differences  14 from placebo in these key clinical milestones  15 of about a day, and up to 2 days at the 75th  16 percentile, corresponding to patients with  17 prolonged POI and likely a higher risk for  18 delayed discharge; a higher proportion of  19 responders achieving GI-2 recovery by Day 5;  20 and hospital discharge prior to Day 7, with  21 corresponding NNTs below 10.  22 These outcomes were supported by</p>	<p style="text-align: right;">61</p> <p>1 agency's request to provide more information  2 about the GSK-sponsored OBD trials and in  3 particular, Study GSK014. Eric.  4 DR. MORTENSEN: Thank you,  5 Dr. Jackson. Eric Mortensen, group director,  6 GlaxoSmithKline, clinical development. And good  7 morning, and thank you to the committee for the  8 chance to present some of our data today.  9 I'll be talking to you today about  10 studies of alvimopan in the setting of OBD,  11 the opioid-induced bowel dysfunction that's  12 frequently observed in patients with chronic  13 opioid use. I'll be focusing most of today's  14 discussion upon the results of a single  15 clinical trial, a long-term safety study,  16 Protocol 014, and I'll conclude with a few  17 remarks from our study in patients with  18 cancer-related pain.  19 Now, opioid bowel dysfunction, or  20 OBD, is a chronic condition characterized by  21 severe constipation and associated symptoms.  22 The patients we studied with OBD were quite</p>

<p style="text-align: right;">62</p> <p>1 distinct from those in the POI population, in  2 that they generally had chronic pain of  3 several years' duration for which they had  4 required much higher doses of opioids than  5 those commonly used in POI for acute  6 analgesia.  7 Now, because long-term exposure to  8 opioids sensitizes patients to the effect of  9 opiate antagonists, patients with OBD were  10 intolerant of the much higher alvimopan doses  11 used in the POI condition, experiencing  12 abdominal cramping and diarrhea. Doses of  13 1 milligram alvimopan increased those  14 symptoms on the first day of treatment of  15 OBD.  16 And for that reason, patients in  17 the OBD program were treated with only 1/2 a  18 milligram alvimopan twice daily as opposed to  19 the proposed dose of 12 milligrams twice  20 daily in the POI indication.  21 Patients in the OBD population  22 suffered a debilitating pain condition for an</p>	<p style="text-align: right;">64</p> <p>1 or placebo at a ratio of 2-to-1. And it  2 should be noted that relative to today's  3 concern about safety, that this study's  4 inclusion criteria did not require baseline  5 chest radiography or electrocardiography.  6 Now, the adverse events will be  7 discussed and consist of three categories:  8 Myocardial infarctions and other significant  9 cardiovascular events, and events that were  10 encoded as either neoplasia or as bone  11 fracture. No imbalance in these events was  12 seen in prior studies, and hence, no  13 pre-specified definitions were established to  14 permit uniform case ascertainment or  15 comparison between treatment groups. We note  16 these events were uncommon, and therefore,  17 risk estimates have very wide confidence  18 intervals.  19 Our review of the various events  20 included careful evaluation of the index  21 cases along with examination of the  22 biological, clinical, and epidemiologic</p>
<p style="text-align: right;">63</p> <p>1 average of greater than 10-1/2 years. They'd  2 required opioid analgesia for these  3 conditions for greater than 7-1/2 years, with  4 a mean total daily dose of opioid that was  5 equivalent to about 232 milligrams of  6 morphine.  7 Now, this was in significant  8 contrast to the experience in the POI  9 condition, where there were generally no  10 underlying pain conditions, and patients  11 received approximately a tenth of this dose  12 of opioid for fewer than two weeks. Per  13 protocol, those patients did not have any  14 significant prior opioid exposure. And the  15 data I'll be presenting today comes from our  16 studies in patients with OBD.  17 Study 014 was a 12-month  18 randomized, double-blind, placebo-controlled  19 trial assessing the effect of alvimopan in  20 patients with chronic non-cancer pain and  21 symptoms of OBD. Patients were randomized to  22 either alvimopan, 1/2 milligram twice daily,</p>	<p style="text-align: right;">65</p> <p>1 plausibility of each event. Exposure  2 response relationships were assessed. And  3 finally, integrated reports were subjected to  4 both internal and external expert review.  5 A global review of the  6 cardiovascular events in Study 014 using  7 categories agreed with the FDA showed low  8 incidence of events on alvimopan, but a  9 numerical increase compared with the absence  10 of events on placebo. This was largely  11 driven by an increase in myocardial  12 infarctions in the alvimopan group.  13 The low frequency of individual  14 events results in the wide confidence  15 intervals seen here around the relative risk  16 estimates. Subsequent assessment showed that  17 all the events of myocardial infarction in  18 the alvimopan patients occurred in those with  19 prior cardiovascular disease, with a  20 clustering of events noted so that 5 of the 7  21 events occurred at 2 of the 232 study sites  22 in the trial.</p>

<p style="text-align: right;">66</p> <p>1 A time-to-event analysis of CV  2 events observed in Study 014 is shown here,  3 and shows the separation versus placebo for  4 the 538 patients on alvimopan. Few  5 cardiovascular events were observed beyond  6 six months, suggesting no accumulation of  7 risk, and no events were observed in the  8 period relevant to postoperative ileus.  9 Importantly, none of the myocardial  10 infarctions, the initial event of concern,  11 occurred at less than 30 days or at more than  12 four months after initiation of study drug.  13 Prior to the observation of the  14 imbalance of Study 014, no evidence of an  15 increase in cardiovascular events was  16 identified from clinical studies at less a  17 duration in essentially the same patient  18 population. This included two studies with  19 three months' duration of drug exposure.  20 Now, focusing upon the adverse  21 event of myocardial infarction, the principal  22 observation of imbalance in the 014 study,</p>	<p style="text-align: right;">68</p> <p>1 the results of Study 014. In particular, the  2 imbalance of myocardial infarctions was less  3 pronounced. And once again, the confidence  4 intervals around the relative risk estimates  5 for individual events are wide, owing to the  6 overall low incidence of events in both  7 groups with all intervals embraced with a  8 value of 1.  9 Now, as I've stated, the lack of  10 pre-specified disease definitions confounded  11 our ability to analyze cardiovascular events.  12 As a result, an independent data monitoring  13 committee was established to provide standard  14 definitions to improve the uniformity of case  15 ascertainment, to review individual cases,  16 and to provide a blinded comparison of the  17 incidences of cardiovascular events across  18 the OBD database.  19 The resulting IDMC's analysis  20 showed no significant difference in the  21 frequency of CV events between alvimopan and  22 placebo, and similarly, no significant</p>
<p style="text-align: right;">67</p> <p>1 these studies showed no association with  2 alvimopan compared with placebo. Again, the  3 number of adverse events are small,  4 reflecting the low incidence rate, and  5 resulting in the wide confidence intervals  6 that we see here around the relative risk  7 estimates.  8 A time-to-event analysis of the  9 cardiovascular events in these other OBD  10 studies of patients with non-cancer pain is  11 shown here. The maximum duration of exposure  12 is here three months, but largely overlaps  13 the period of accumulation of cardiovascular  14 events in Study 014. Here, with a larger  15 population of 1,190 patients exposed to  16 alvimopan, the curve showed no separation  17 from placebo with respect to incidence.  18 A combination of these CV events  19 from the OBD program in non-cancer pain is  20 shown here. After integrating all data, we  21 saw a persistent but lesser imbalance of  22 cardiovascular events, primarily driven by</p>	<p style="text-align: right;">69</p> <p>1 difference was observed in either ischemic or  2 non-ischemic cardiovascular events.  3 Recognizing the limitation of  4 making conclusions from adverse event  5 reports, the IDMC concluded that the risk of  6 ischemic heart disease with alvimopan  7 exposure was largely discharged.  8 Furthermore, they found no  9 significant evidence of an elevation in the  10 incidence of other or non-ischemic  11 cardiovascular events with alvimopan versus  12 placebo. Nonetheless, they suggested that a  13 further study be conducted in the OBD  14 population to confirm these observations, and  15 that any studies should include an enhanced  16 monitoring of cardiovascular events and IDMC  17 oversight to confirm this interpretation.  18 Following the completion of  19 Study 014, a second imbalance was observed  20 with respect to the number of adverse events  21 encoded as neoplasm. The incidence rates  22 following the inclusion of an additional case</p>

70	<p>1 reported post-study are also shown here. And</p> <p>2 I think the change in the relative risks seen</p> <p>3 with this addition shows how this value is</p> <p>4 being driven by very small numbers of events.</p> <p>5 A review of individual case reports</p> <p>6 shows this group encoded as neoplasm was</p> <p>7 quite heterogeneous, including some instances</p> <p>8 as post-traumatic neuroma, lipoma, benign</p> <p>9 hair follicle tumor that are not</p> <p>10 pre-malignant and do not show clinical</p> <p>11 development or progression. The range of</p> <p>12 lesions was also considered to be atypical</p> <p>13 for an agent with primary or secondary</p> <p>14 carcinogenic potential.</p> <p>15 Now, given questions about the</p> <p>16 clinical meaningfulness of the range of</p> <p>17 events in this broad grouping, we'll examine</p> <p>18 those events of malignant neoplasm to assess</p> <p>19 potential treatment and balance. Adverse</p> <p>20 events associated with significant risk of</p> <p>21 malignancy were identified without respect to</p> <p>22 drug treatment. The separations were then</p>	72	<p>1 relative risk, but also approximates the NULL</p> <p>2 value, and with little difference in the</p> <p>3 distribution of cases.</p> <p>4 To further explore the potential</p> <p>5 observed imbalance of neoplastic events in</p> <p>6 the non-cancer OBD studies, an examination</p> <p>7 was conducted of results from a study in</p> <p>8 patients with cancer-related pain requiring</p> <p>9 an opioid analgesia. Study 008 and its</p> <p>10 extension 101684 were intended to assess the</p> <p>11 effect of alvimopan in patients with</p> <p>12 cancer-related pain requiring opioid</p> <p>13 analgesia and with symptoms of OBD.</p> <p>14 Eligible patients were randomized</p> <p>15 unequally to placebo or 1 of 3 doses of</p> <p>16 alvimopan at a ratio of approximately</p> <p>17 2.5-to-1 alvimopan to placebo by study's end.</p> <p>18 Patients completing the three-week efficacy</p> <p>19 trial were allowed to continue with their</p> <p>20 assigned treatment for as long as they</p> <p>21 desired.</p> <p>22 Like most palliative care studies,</p>
71	<p>1 assessed by an advisory committee of external</p> <p>2 oncologists for consistency. Apart from</p> <p>3 minor differences between the FDA and GSK</p> <p>4 with respect to classification, there was</p> <p>5 general agreement for all events classified</p> <p>6 as malignant.</p> <p>7 Here, we see that malignancies</p> <p>8 constitute a small number of the cases, that</p> <p>9 the relative risk estimates are modest, while</p> <p>10 confidence levels all embrace the NULL value.</p> <p>11 With the inclusion of Study 014 of the</p> <p>12 additional unsolicited neoplastic adverse</p> <p>13 event reported post-study, we see the</p> <p>14 perceived imbalances further diminished.</p> <p>15 These imbalances of the militant</p> <p>16 neoplasm were significantly affected by the</p> <p>17 small number of events in the safety</p> <p>18 database, and the likelihood that several</p> <p>19 patients may apparently have had pre-existing</p> <p>20 lesions prior to randomization. We see in</p> <p>21 the third line the inclusion of all cases</p> <p>22 from all non-cancer OBD studies produces a</p>	73	<p>1 Study 001 predominantly selected patients</p> <p>2 with advanced disease and a high likelihood</p> <p>3 of mortality. Enrollment of eligible</p> <p>4 patients was challenging, given the</p> <p>5 limitations that many patients with severe</p> <p>6 illness had in providing detailed study</p> <p>7 reports of their symptoms. Of note, this</p> <p>8 study was not designed to measure the</p> <p>9 progression of patients' underlying cancer</p> <p>10 diagnosis, nor to ensure that prognostic</p> <p>11 factors for disease progression were balanced</p> <p>12 between the treatment groups.</p> <p>13 As a conservative clinical</p> <p>14 assessment then, we therefore compared the</p> <p>15 number of deaths by treatment group. In this</p> <p>16 population, we saw a numeric imbalance for</p> <p>17 deaths, with 20 patients in the alvimopan</p> <p>18 group compared with 3 on placebo. We have,</p> <p>19 however, provided a detailed analysis in the</p> <p>20 briefing document that examines potential</p> <p>21 reasons for these findings.</p> <p>22 These demonstrate the total</p>

<p style="text-align: right;">74</p> <p>1 exposure to study agent was much greater in  2 the alvimopan group. Furthermore, subjects  3 in the alvimopan arm had markers of more  4 advanced disease than subjects on placebo.  5 Overall, our analysis indicated that  6 alvimopan exposure was not the significant  7 predictor for death, and suggested the  8 patients' experience of potential drug  9 efficacy may have led to the greater  10 retention of patients in the alvimopan group  11 for the extension study.  12 Finally, the observation of an  13 imbalance in bone fractures are summarized  14 here. There was an excess of fractures  15 reported among alvimopan users in the 014  16 study. Based upon the evaluation of all data  17 across all OBD studies in cancer and  18 non-cancer subjects, this finding appears to  19 be limited to Study 014.  20 The assessment of events in the OBD  21 studies was hampered by the lack of  22 perspective defined fracture criteria and a</p>	<p style="text-align: right;">76</p> <p>1 long-term trial, and were not replicated in  2 other OBD or POI studies.  3 Now, based upon these findings, the  4 preclinical data were reviewed for any  5 potential association. With respect to  6 cardiovascular events, the preclinical  7 program failed to identify any evidence of  8 cardiotoxicity. Similarly, monitoring of  9 cardiac function during clinical pharmacology  10 studies demonstrated no negative cardiac  11 effects. In addition, preclinical  12 assessments of alvimopan, including  13 clastogenicity, mutagenicity, and  14 carcinogenicity assays, were all negative.  15 Definitive QT studies in humans  16 showed no effect at doses up to 24 milligrams  17 given twice daily. An evaluation of exposure  18 response relationships showed no relationship  19 between levels of alvimopan and either  20 cardiovascular events, neoplasia, or  21 fractures. Overall, preclinical and clinical  22 data do not suggest a clear pattern of either</p>
<p style="text-align: right;">75</p> <p>1 lack of collection of radiography. No  2 negative action was identified to explain  3 these findings, and studies of other  4 opioid-receptor antagonists have not  5 identified any effects on bone metabolism.  6 In summary, we believe that no  7 confirmed association between drug exposure  8 and any of the adverse events has been  9 established. The OBD population is in  10 general at high risk for each of these  11 problems. The presence of hypertension,  12 hyperlipidemia, and tobacco use increases the  13 risk of cardiovascular events. Tobacco use  14 is further associated with aero-digestive  15 cancers. Opioid users have an increased risk  16 of falls and often use concomitant  17 medications associated with osteopenia.  18 In each case, the frequency of  19 events was low, and the relative risk  20 estimates uniformly included the NULL value.  21 Finally, we see that these events were  22 principally confined to Study 014, a</p>	<p style="text-align: right;">77</p> <p>1 beneficial or deleterious effects on  2 cardiovascular function, neoplasia, or bone  3 metabolism as associated with long-term  4 treatment with opioid agonists or  5 antagonists.  6 In summary, the findings of  7 interest were primarily related to a single  8 study in the OBD patient population. These  9 findings did not reflect the experience of  10 other OBD studies, nor did the time to these  11 events generally overlap the period for  12 treatment of the proposed indication of POI.  13 With respect to the risk of  14 ischemic heart disease, the independent  15 monitoring committee concluded that the  16 available data indicated that the risk for  17 treatment effect had been largely discharged.  18 While the clinical significance of  19 these findings remains unclear, we recognize  20 these observations require further  21 investigation in the OBD population to fully  22 establish the safety of long-term</p>

78	<p>1 administration of alvimopan. These findings  2 have not ever been replicated in shorter term  3 studies of alvimopan in either the OBD or the  4 POI populations.</p> <p>5 With that then, I'll turn things  6 back over to Dr. Jackson to complete the  7 discussion of the POI safety program.</p> <p>8 DR. JACKSON: Thank you,  9 Dr. Mortensen. So now, if we may turn our  10 attention back to the POI safety database. I'm  11 going to address the following four points,  12 including the safety follow-up in the POI  13 studies.</p> <p>14 The POI safety database includes  15 nearly 4,000 patients worldwide. It consists  16 of, as you've seen, three Phase II studies  17 and six Phase III studies. This database  18 includes all patients who underwent bowel  19 resection or total abdominal hysterectomy and  20 who received at least one dose of 1, 3, 6, or  21 12 milligrams of alvimopan or placebo.  22 Disposition of these patients, as you've seen</p>	80	<p>1 Focusing on serious adverse events,  2 overall rates were low. The most common  3 serious adverse events were POI and small  4 intestinal obstruction, which are, as you may  5 know, often difficult to differentiate in  6 this setting, both of which were less  7 frequent in the alvimopan group. SAEs  8 resulting in death were rare and comparable  9 between groups.</p> <p>10 Now, because of the numerical  11 imbalance of myocardial infarctions in  12 GSK014, the agency asked us to provide  13 additional documentation, such as ECG  14 tracings and cardiac biomarkers for POI  15 patients who had a cardiovascular event of  16 interest. Both the agency and Adolor used  17 these additional data to adjudicate and  18 categorize these cardiovascular events as  19 noted here, to determine if any imbalances  20 existed.</p> <p>21 The rates for these CV events of  22 interest were low, and there was no evidence</p>
79	<p>1 already, shows that approximately 80 percent  2 completed treatment, and about 8 to  3 11 percent discontinued as a result of an  4 adverse event. It's worth noting, I think,  5 that fewer patients treated with 6 or  6 12 milligrams discontinued due to adverse  7 events. Now, because very few patients  8 received doses of 1 or 3 milligrams of  9 alvimopan in these studies, this is the last  10 time I will discuss this group.</p> <p>11 As you would expect, following  12 major abdominal surgery, the most commonly  13 reported treatment-emergent adverse events  14 were nausea and vomiting. And as you can see  15 here, the frequency of nausea, vomiting,  16 abdominal distension, pyrexia, and  17 hypertension were essentially comparable  18 across the treatment groups. Less common  19 events occurring with a frequency of less  20 than 10 percent in any group also showed  21 comparable frequency across the treatment  22 groups.</p>	81	<p>1 of an increase in cardiovascular events among  2 the alvimopan group. Because event rates  3 were low, the 95 percent confidence intervals  4 surrounding the relative risks are generally  5 wide. And when we combine all cardiovascular  6 events of interest in the second line here  7 into a single category, we see that the  8 incidence is somewhat lower in the alvimopan  9 group.</p> <p>10 To provide further assessment, we  11 also sought an independent analysis from the  12 Duke Clinical Research Institute Clinical  13 Events Committee, the team of practicing  14 physicians specializing in cardiology or  15 neurology. Now, they provided a blinded  16 adjudication of all POI cardiovascular  17 adverse events using patient-level source  18 documents. The DCRI used the American Heart  19 Association, American College of Cardiology,  20 guidelines, as well as clinical judgment to  21 define specific events. Hence, their numbers  22 differ slightly from the Adolor analysis, but</p>

<p style="text-align: right;">82</p> <p>1 the results confirm no imbalance in CV events  2 exists between the two treatment groups.  3 In addition to the Adolor and Duke  4 analyses, we also looked for references in  5 the literature regarding the incidence of  6 myocardial infarction following a bowel  7 resection. The data shown here are from a  8 paper by Khuri et al. using the NSQIP  9 database, the VA database. And we see that  10 the observed incidence of myocardial infarcs  11 in our POI trials was generally consistent  12 with that shown in this very large database  13 of bowel resection patients.  14 Turning to the secondary category  15 of imbalance seen in the GSK014 study of OBD  16 patients' bone fractures, we saw only one in  17 the POI database.  18 And finally, looking here at  19 treatment-emergent malignant neoplasia in the  20 POI studies, the incident of neoplasia was  21 low and balanced between the groups.  22 Now, a question has been raised</p>	<p style="text-align: right;">84</p> <p>1 again, that metabolite concentrations may be  2 significant beyond this observation time.  3 But, in fact, by six-plus days following the  4 last dose, metabolite levels are negligible.  5 Therefore, we believe that the follow-up  6 safety monitoring in the POI population was  7 appropriate and was comprehensive.  8 In summary, alvimopan 12 milligrams  9 was well-tolerated. There's no evidence of  10 increased cardiovascular, fracture, or cancer  11 risk seen in this large clinical safety  12 database. As Dr. Techner noted earlier,  13 there was no evidence of a reversal of opioid  14 analgesia with alvimopan. Collectively, the  15 efficacy, morbidity, and safety results  16 you've seen today we believe support a  17 positive benefit-risk profile for the use of  18 alvimopan 12 milligrams in patients  19 undergoing bowel resection.  20 I would now like to turn to and  21 provide an outline of our proposed risk  22 management plan. In November 2006, we</p>
<p style="text-align: right;">83</p> <p>1 regarding the adequacy of follow-up in the  2 POI studies to detect later adverse events.  3 We're confident in the quality of our data,  4 given that 88 percent of the patients in the  5 worldwide POI safety database were followed  6 up after their last dose of medication.  7 Three-quarters were contacted by telephone,  8 most at one to two weeks, to ask about  9 adverse events. Another 13 percent had a  10 follow-up visit with the surgeon. And in  11 Study 001, there was also a six-week  12 follow-up visit where 76 percent of patients  13 were seen and questions were asked about  14 adverse events.  15 In the North American studies, site  16 visits by monitors assessed all follow-up  17 data for 30 days after the last dose by  18 review of records. Bowel resection patients,  19 as you heard from Dr. Techner, are routinely  20 seen by the surgeon and evaluated, usually  21 within two to four weeks for an initial  22 postop visit. And it has been suggested,</p>	<p style="text-align: right;">85</p> <p>1 received an approvable action letter  2 requesting that we provide a risk management  3 plan to address possible cardiovascular risk  4 of longer term exposure, and to minimize  5 off-label use.  6 With this risk management plan, our  7 primary goal is to ensure appropriate use of  8 Entereg, and to prevent any use of Entereg  9 outside of the hospital.  10 We recognize the importance of  11 providing Entereg within the proposed  12 indication, because POI is an unmet medical  13 need. There is no approved pharmacological  14 option available for patients or for those  15 who care for them. In addition, I think it's  16 clear from the data presented today that  17 Entereg provides clinically meaningful  18 benefit to patients undergoing bowel  19 resection without an increased risk of  20 adverse effects.  21 Now, in our evaluation of the  22 various different options, other</p>

86	<p>1 considerations were also important. The dose 2 of Entereg which will be available for the 3 management of POI is 12 milligrams. The 4 potential for inappropriate use of Entereg 5 outside of the hospital would be in patients 6 already receiving opioids.</p> <p>7 From our data, we know that 8 opioid-tolerant patients who receive 9 3 milligrams or greater experience 10 gastrointestinal side effects that would make 11 it highly unlikely that they would want to 12 use a 12-milligram dose again. We also know 13 that the physical-chemical properties of the 14 12-milligram formulation make it very 15 difficult to divide it into smaller doses. 16 These facts make it unlikely that the 17 12-milligram capsule would be used outside of 18 the hospital.</p> <p>19 In addition, we know from past 20 experience that limiting distribution from 21 the wholesaler can significantly reduce 22 inappropriate distribution. However, the</p>	88	<p>1 pharmacists that Entereg is for hospital use 2 only and should not be used outside of that 3 setting.</p> <p>4 We plan to institute systems to 5 monitor compliance with these requirements, 6 and these will include daily reports from 7 wholesalers detailing where Entereg was 8 shipped. In the event of a shipment to an 9 non-approved pharmacy, we will take immediate 10 corrective action. The use of this approach 11 has already been applied by others in the 12 industry, and has resulted in a high rate of 13 compliance, ensuring that the product reached 14 the appropriate end user in over 99 percent 15 of shipments.</p> <p>16 The second component of our risk 17 management proposal is our professional 18 labeling. We're proposing that the numerical 19 imbalance in myocardial infarcs from GSK014 20 be described in the Warnings and Precautions 21 section of the label. In addition, the 22 proposed label is very specific about where</p>
87	<p>1 process employed for this type of 2 distribution should not be overly burdensome 3 for the health care system, and we want to 4 make sure that Entereg is readily available 5 for those patients who will benefit from its 6 use.</p> <p>7 Therefore, our risk management plan 8 comprises four components. Each of these 9 serves a specific function, and they need 10 then to be considered in totality.</p> <p>11 The first and most important 12 component will be the distribution process. 13 We will not distribute samples. We will put 14 contracts in place that require wholesalers 15 only to distribute to acute care hospitals 16 identified in their databases. Wholesalers 17 will place an NDC block on Entereg, which 18 will remove Entereg as an ordering option for 19 retail pharmacies.</p> <p>20 In the unlikely event that Entereg 21 should reach a retail pharmacy, the major 22 pharmacy information systems would alert the</p>	89	<p>1 the drug should or should not be used. 2 Specifically, we state that Entereg is 3 contraindicated in patients who have received 4 prior opioids for more than seven consecutive 5 days. The Warnings and Precautions section 6 also describes the most common 7 gastrointestinal adverse events that would 8 occur in opioid-tolerant patients.</p> <p>9 Entereg is limited to seven days or 10 15 doses in the hospital only. And we have 11 highlighted our professional labeling and 12 modified our packaging, both the blister and 13 the carton, so that it clearly states, 14 "hospital use only."</p> <p>15 Our educational effort will be 16 directed at health care providers involved in 17 the management of bowel resection patients, 18 who will be in strict compliance with the 19 approved label, reinforcing that Entereg 20 should be used in the hospital only. In 21 addition, promotional efforts will also be 22 directed only to the appropriate professional</p>

90	<p>1 audience involved in the care of bowel  2 resection patients. We will have our  3 hospital sales force visit hospital  4 outpatient pharmacies to ensure that that  5 they are aware that Entereg should not be  6 dispensed. And we feel that through this  7 risk management plan, we can safely provide  8 access to Entereg in the hospital, thus  9 meeting an unmet clinical need without  10 placing an unnecessary burden on the health  11 care system.</p> <p>12 In summary, the data from the  13 extensive development program of Entereg  14 clearly demonstrate a clinically meaningful  15 acceleration of GI recovery, resulting in  16 fewer patients with prolonged hospital stays.</p> <p>17 Dr. Senagore has illustrated the  18 benefits associated with early resolution of  19 POI. These include fewer postoperative  20 nasogastric tube insertions, fewer patients  21 with prolonged hospital stays, and a marked  22 reduction in all-cause readmissions within 10</p>	92	<p>1 indication we proposed at the beginning.  2 This concludes the sponsor  3 presentation. Mr. Chairman, ladies and  4 gentlemen, I thank you for your attention.</p> <p>5 DR. BUCHMAN: We're going to now open  6 the discussion to questions for the sponsor.  7 Members of the committee who have questions for  8 the sponsor, please raise your hand and make  9 sure when you speak that you press the red  10 button on your microphone.</p> <p>11 Dr. Talamini?  12 DR. TALAMINI: Mark Talamini,  13 University of California at San Diego. I'm a  14 temporary voting member. I'd like to commend  15 the company for an excellent presentation and a  16 set of data beforehand as well, as well as the  17 FDA preparation package was terrific. A couple  18 of questions, and I'll ask them all at once.</p> <p>19 In your protocols, were there any  20 aspects of the surgical procedure itself that  21 were part of the protocol, such as how the  22 anastomosis is done or how the operations</p>
91	<p>1 days of hospital discharge. This meaningful  2 improvement was observed in addition to an  3 accelerated care pathway without any  4 significant safety issues in the POI  5 population.</p> <p>6 The numerical imbalances observed  7 in the OBD study, GSK014, were unprecedented  8 and not seen in the other OBD studies. Given  9 that these events occurred in a time period  10 not relevant to POI, and that no plausible  11 explanation for their occurrence has been  12 identified, we feel that Entereg is safe for  13 use in the management of postoperative ileus.</p> <p>14 However, to ensure that Entereg is  15 appropriately used, we are proposing a risk  16 management plan that will limit the use of  17 Entereg to the hospital and keep it out of  18 the retail space.</p> <p>19 As a result, we believe that  20 Entereg represents a favorable and compelling  21 benefit-risk profile, which makes it  22 appropriate to market alvimopan for the</p>	93	<p>1 were conducted, or was that simply at the  2 surgeon's discretion? So that's one  3 question.</p> <p>4 The second question, in all of your  5 postoperative ileus study patients, I believe  6 they were all screened with EKGs and chest  7 X-rays. But in your risk management or  8 risk -- this most recent aspect that you  9 discussed, are you proposing that that also  10 be a screen for all patients who receive this  11 drug if it's approved? I guess it's just  12 those two questions right now.</p> <p>13 DR. JACKSON: Thank you, Dr. Talamini.  14 If I could take the second question first, and  15 then I'm going to ask Dr. Techner to come up and  16 address the surgical issues.</p> <p>17 We are not proposing that the label  18 currently contain recommendations in regard  19 to clinical management, but certainly, as you  20 well know, all of these patients undergoing  21 elective surgery do have pretty extensive  22 work-up as part of their preoperative</p>

94	<p>1 evaluation. And we did not see anything in 2 the clinical studies suggesting changes in 3 EKG between the alvimopan and placebo groups. 4 Dr. Techner? 5 DR. TECHNER: Lee Techner, Adolor. To 6 address the first part of your question, the 7 answer is no. There was no standardized 8 surgical procedure or standardized methodology 9 for the anastomosis across the clinical trials. 10 That was basically left to the discretion of the 11 surgeon, and of course, I would assume, based on 12 the clinical condition. 13 DR. BUCHMAN: Dr. Kramer, did you have 14 some questions or comments? 15 DR. KRAMER: Dr. Judith Kramer, Duke 16 University. Dr. Techner I think probably might 17 want to answer this. As a competitive 18 antagonist of the mu-opioid receptor, I would 19 have thought that a strong predictor of 20 alvimopan's GI effects would be the dose of 21 concomitant opioids administered. Yet I didn't 22 see an attempt to quantify the dose in any way</p>	96	<p>1 getting virtually very low doses to patients 2 getting very, very high doses. So we have 3 not been able to see that across any of our 4 clinical trials. 5 But what we have been able to see, 6 I'll show you this right now, is that for the 7 vast majority of patients who received opioid 8 IV PCA, the choice of opioid was morphine. 9 That was in approximately 90 percent of 10 patients. And what you see here is the GI-2 11 Kaplan-Meier recovery curve in those patients 12 who did receive IV morphine. And I think you 13 can see here that the curves look very 14 similar to what I showed you before. So we 15 see the alvimopan treatment group always to 16 the left of the placebo treatment group, and 17 the magnitude of effect, as we represent by 18 the Kaplan-Meier curve across the observation 19 period, is about the same. 20 DR. KRAMER: You said that you looked 21 very carefully at those, but is there any reason 22 that you didn't quantify the quintiles of dose</p>
95	<p>1 and look at that in a multivariable analysis for 2 the effect -- on peripheral effects on the GI 3 system or the GI endpoints. 4 Could you comment on that? 5 DR. TECHNER: Sure I could. We have 6 looked extensively to see whether or not there's 7 any relationship between dose of opioid used and 8 pharmacologic effect. We have evaluated the 9 current POI database to see whether or not we 10 could determine if there's any threshold that 11 one needs to achieve with respect to opioid 12 dose, and thus produce either a more or less 13 robust response. 14 What we have found is we have not 15 been able to determine that type of 16 relationship or demonstrate one. And I think 17 the reason for that is, certainly in the 18 U.S., the vast majority of patients are 19 receiving a fairly consistent amount of 20 opioid-based IV PCA, at least within the 21 first 48 to 72 hours following surgery. So 22 you don't get that broad range of patients</p>	97	<p>1 and look at that as a covariate endpoint? 2 DR. TECHNER: We have done that. And 3 again, in doing so, we did not see any 4 relationship, even looking at quartiles or even 5 looking at opioid consumption in other ways, a 6 relationship between opioid dose and response. 7 DR. KRAMER: And yet in the European 8 trial where you had an opioid-sparing approach, 9 you were not able to demonstrate a benefit? 10 DR. TECHNER: In the European 11 Study 001, we had certainly more patients using 12 opioid-sparing technique. And I think what we 13 saw there, as I showed you in the core slide, is 14 that when we look at GI-2, the endpoint that I 15 believe we and FDA feel is a more reasonable 16 endpoint with respect to assessing the treatment 17 effect in patients undergoing bowel resection, 18 although it was somewhat less robust, it was 19 still a statistically significant effect. 20 DR. KRAMER: But about four hours. 21 DR. TECHNER: Excuse me? 22 DR. KRAMER: But more on the order of</p>

98	<p>1 4 hours difference rather than 24 hours.</p> <p>2 DR. TECHNER: Well, it depends on what</p> <p>3 measure you're looking at, yes.</p> <p>4 DR. KRAMER: One last question. Given</p> <p>5 that your successful efficacy studies all</p> <p>6 required planned PCA, and the one study that</p> <p>7 didn't require it, the European study, was</p> <p>8 negative, will your label specify that this</p> <p>9 should only be used in patients getting opioid</p> <p>10 postop PCA?</p> <p>11 DR. TECHNER: Well, I'll address your</p> <p>12 question in two parts. One, I don't believe</p> <p>13 that -- certainly we don't believe that</p> <p>14 Study 001 was a negative study. I think when</p> <p>15 you look at the GI recovery endpoint by GI-2, as</p> <p>16 we've just said, it is statistically</p> <p>17 significant, and the mean and median differences</p> <p>18 are all favoring alvimopan. So that's number</p> <p>19 one.</p> <p>20 Number two is with respect to the</p> <p>21 label, we have not really negotiated with FDA</p> <p>22 the label at this point. They have our</p>	100
99	<p>1 proposed label, and certainly we are willing</p> <p>2 to discuss things like this that would be</p> <p>3 appropriate.</p> <p>4 DR. BUCHMAN: Dr. Pasricha?</p> <p>5 DR. PASRICHA: Thank you. Jay</p> <p>6 Pasricha, Stanford. I have several questions,</p> <p>7 and I'll ask them one at a time. First is a</p> <p>8 follow-up on the issue of the mechanism of</p> <p>9 action. I think the emphasis so far has been</p> <p>10 that this is primarily due to antagonism of</p> <p>11 exogenous opioids, but it's true that it also</p> <p>12 has some intrinsic motility effect.</p> <p>13 And some of the discrepancies that</p> <p>14 you're seeing between the doses of morphine</p> <p>15 and the effect, and particularly the lack of</p> <p>16 efficacy in the transabdominal hysterectomy</p> <p>17 group, may be because what's at play here.</p> <p>18 The underlying pathophysiology is not so much</p> <p>19 due to exogenous opioids, but activation of</p> <p>20 endogenous opioid systems.</p> <p>21 So I wonder if you have any</p> <p>22 comments on that, and I'll go on to my other</p>	101

<p style="text-align: right;">102</p> <p>1 complications related to that? And have you  2 shown a benefit of your drug with respect to  3 those non-POI hospital complications? Which  4 is really implied, but I'm not sure has been  5 actually demonstrated.</p> <p>6 DR. TECHNER: Yeah. I think that gets  7 at a very important question, and certainly one  8 that we are very interested in. And I think you  9 have to take a couple things into consideration.</p> <p>10 One, the studies really weren't  11 designed to evaluate differences in those  12 types of events between the active groups and  13 placebo. So that's number one.</p> <p>14 Number two is we don't have  15 predefined or prespecified definitions for  16 those events. However, we did look at that,  17 and we did try to see what potential effect  18 we may have on those more common nosocomial  19 complications. And let's show you that now.</p> <p>20 So what we did was we looked at  21 several categories. One, thromboembolic  22 events, DVT-PE, and also under a broad</p>	<p style="text-align: right;">104</p> <p>1 from his clinical perspective. Yes?</p> <p>2 DR. PASRICHA: So related to that,  3 your all-cause readmission rate was higher in  4 the placebo group?</p> <p>5 DR. TECHNER: That's correct.</p> <p>6 DR. PASRICHA: Did you analyze by  7 category of --</p> <p>8 DR. TECHNER: Yes.</p> <p>9 DR. PASRICHA: And what did you find?</p> <p>10 DR. TECHNER: Yes, let's show you that  11 as well. All-cause readmissions broken down by  12 category. Now, again, understanding the caveats  13 that I mentioned before, we look at the events  14 that were classified by the physician, by the  15 investigator, as the primary cause for  16 readmission.</p> <p>17 And what you can see here is we've  18 broken these out into three categories: GI  19 events, surgical complications, and the  20 category of other. And I think when you look  21 down this list you can see that postoperative  22 ileus, certainly the readmission for POI as</p>
<p style="text-align: right;">103</p> <p>1 category of postoperative infection, we  2 looked at wound infection, respiratory tract  3 infections, sepsis, and UTI.</p> <p>4 Now, one thing you'll notice here  5 immediately is that the event rate for these  6 are quite low. I think part of that is  7 related to the fact that, at least these  8 days, in the preoperative arena, surgeons  9 will aggressively try and prophylax for all  10 of these events. But what you do see here is  11 that the incidence of these events is low and  12 it's comparable. However, there is a  13 trend -- when you look here, particularly in  14 the broad category of postoperative  15 infection, that the incidence is lower in the  16 active treatment groups. And that pretty  17 much pertains across the board.</p> <p>18 So that is the extent to which we  19 have tried to get at the point that you're  20 getting to. But what I'd like to do to try  21 and elaborate even further is I'd like to  22 bring up Dr. Senagore so that he can address</p>	<p style="text-align: right;">105</p> <p>1 per the investigator, was lower in the  2 12-milligram group as compared to the placebo  3 group.</p> <p>4 Same thing for readmission for  5 vomiting. Now, it's difficult to ascertain  6 what the underlying diagnosis was there. I  7 mean, this could represent unresolved ileus  8 as well. Interestingly, when you look at  9 anastomotic leak, you see a lower readmission  10 rate for an anastomotic leak in the  11 12-milligram group, and same thing with  12 postoperative abscess. I think everything  13 else is fairly comparable.</p> <p>14 So yes, we have tried to break this  15 down and see where the trends may be. And  16 what we conclude from this, realizing that  17 the event rate is low and realizing the  18 trials really weren't prespecified and  19 designed to look at this, that it looks as  20 though that there's a tendency for a lower  21 readmission rate when the readmission is  22 caused by a GI complication, if you will, in</p>

<p style="text-align: right;">106</p> <p>1 the Entereg group versus placebo. And again,  2 I'll caveat that by we certainly understand  3 these rates are low and we can't draw any  4 definitive conclusions, but we are certainly  5 interested in looking at this.  6 DR. BUCHMAN: I'm going to ask a  7 follow-up question on that particular issue.  8 You showed the data on readmissions, but the  9 premise is that if a patient is discharged from  10 the hospital earlier, there would be a lower  11 risk of nosocomial infections. The previous  12 slide showed postoperative complications related  13 in some way to the operation.  14 We know that there's an epidemic of  15 Clostridium difficile within the hospitals.  16 You had virtually no one who was readmitted  17 for that. But what about during the  18 admission in which they had their surgery?  19 Did you see a difference in either aspiration  20 pneumonias or in Clostridium difficile  21 toxin-positive patients between treatment and  22 placebo groups?</p>	<p style="text-align: right;">108</p> <p>1 question, and I think that I'd like to bring  2 Dr. Senagore up here to answer that question  3 based on his clinical experience directly with  4 these patients.  5 Tony?  6 DR. SENAGORE: I think your question's  7 focused on -- there is a strategy now to examine  8 postoperative pain management more aggressively  9 than we may have in the past. And there is a  10 much broader application of narcotic analgesia,  11 at least in the States, for that. And so the  12 data you saw here was for a very focused  13 application in a very structured enhanced  14 recovery program. If you look at hospitals  15 across the States, you'll probably see much  16 higher doses of narcotics administered to the  17 postoperative patients in a variety of forms.  18 So the hope would be that these data would  19 actually be replicated and enhanced by showing  20 even a greater advantage for the patients that  21 receive alvimopan.  22 DR. BUCHMAN: Dr. Chang?</p>
<p style="text-align: right;">107</p> <p>1 DR. TECHNER: Yeah, it's an  2 interesting question, and we have looked at  3 that. And the answer to your question is no, we  4 did not see any differences in either of those  5 events in the data that we have. Now, again,  6 the event rates are low, so it's hard to draw  7 any conclusions. But the bottom line is we did  8 not see any differences there.  9 DR. BUCHMAN: Dr. Rosing, did you have  10 a question?  11 Ms. Corkery-DeLuca?  12 MS. CORKERY-DeLUCA: Dr. Techner, I  13 was reading a recent journal, JAMA, and they had  14 an article, and the article's on rise of opioid  15 use in surgery. Not being a doctor, doesn't  16 that mean that the morphine would keep you in  17 the hospital longer?  18 So are you saying that the  19 alvimopan would get -- by even the one day,  20 would be a better alternative than to the  21 increased opioid use and morphine?  22 DR. TECHNER: That's an interesting</p>	<p style="text-align: right;">109</p> <p>1 DR. CHANG: Hi. Lin Chang, UCLA. I  2 was just trying to get a better feel for what's  3 the applicability of the side effect profile in  4 the longer term opioid bowel dysfunction  5 studies, and how it's applicable actually to the  6 POI population. So I was wondering if you  7 looked carefully at the patients who did get  8 cardiovascular events in the POI population, if  9 they at all have any similarities to the opioid  10 bowel dysfunction patients who had  11 cardiovascular?  12 For example, did they have any  13 cardiovascular risk factors? Had they been  14 previously on opioids, not in the seven days  15 before the study, but in the past? I mean,  16 is there any -- because the risk management  17 plan isn't going to exclude anybody with a  18 pre-existing condition. So I just wanted to  19 know, are there some people at risk, or do  20 you really believe that you get the side  21 effects because you're on opioids longer,  22 that there's something different in the</p>

110	<p>1 opioid bowel dysfunction patients having  2 long-term opioid use with either metabolism  3 or something like that?  4 DR. JACKSON: Thank you. Firstly, in  5 regard to the imbalance in cardiovascular  6 effects that we did see in the OBD patients,  7 largely confined to Study 014 and -- as you saw  8 from Dr. Mortensen's data, not replicated in the  9 other studies that essentially covered  10 90 percent of that same period for the  11 myocardial infarctions, we did not, I believe,  12 see anything different about the patients in  13 Study 014 that might have accounted for this.  14 In terms of the POI database, we  15 did indeed look for established  16 cardiovascular disease and cardiovascular  17 risk factors, both in the placebo and the  18 alvimopan population. If we focus over here  19 primarily on the bowel resection subjects, it  20 was interesting that there is no imbalance in  21 terms of cardiovascular adverse events, but  22 established cardiovascular disease just</p>	112	<p>1 in and of itself is almost somewhat of a  2 protective mechanism, we believe.  3 DR. BUCHMAN: Dr. Levine?  4 DR. LEVINE: I just wanted to go ask  5 you a little bit about dose response actions as  6 far as the primary goals that you had on  7 solids-in and solids-out, which you didn't show  8 so much here. But in the studies that  9 previously you showed from your publications on  10 314, and in 313 and on 308, the 6-milligram dose  11 for solids-in/solids-out it was .01, the P  12 value, .05 for the 12-milligram. It was .001  13 for the 12 in 313 and .05. And in the -- there  14 was a difference of about seven hours in the  15 313, which was the published paper. Putting it  16 all together, you showed the pharmacokinetic  17 data, that certainly it sounded like the  18 12-milligram had overall better efficacy.  19 Do you feel confident that there is  20 a dose-response curve in any of these primary  21 or secondary endpoints, including hospital  22 discharge, between 6 milligrams and</p>
111	<p>1 turned out to be a little higher in the  2 alvimopan patients.  3 The sorts of things we saw are  4 those you would expect. Smoking was perhaps  5 a little less frequent than the U.S. common  6 numbers, and it's certainly much less than we  7 saw in OBD Study 014, where Dr. Mortensen  8 said about 40 percent of those patients were  9 smokers.  10 Apart from that, we really don't  11 see anything in here that is predictive other  12 than age.  13 DR. TECHNER: If I just might add one  14 thing here. I think it's important to keep in  15 mind that these patients, as you know, are going  16 to undergo, as I believe Dr. Jackson said, a  17 fairly aggressive preoperative screening  18 program. They're undergoing major abdominal  19 surgery. And as such, we would expect that  20 patients at high cardiovascular risk would not  21 be cleared, particularly from a cardiology  22 perspective, to undergo such a surgery. So that</p>	113	<p>1 12 milligrams?  2 DR. JACKSON: Dr. Techner, I'm going  3 to ask to provide a more detailed response, but  4 essentially from my clinical perspective, there  5 is a subtle dose-response curve. You've got to  6 look in specific places for it to establish the  7 12 milligrams as superior to the 6. And maybe,  8 Lee, you would --  9 DR. TECHNER: Sure. Interesting  10 point, and we have looked at this carefully. I  11 think to take the last part of your question  12 first, to establish that up front, we do feel  13 confident that the 12-milligram dose is the  14 appropriate dose in this population. There are  15 several perspectives we look at, as I was  16 discussing with you before.  17 One is the PK perspective. So we  18 do see a higher plasma concentration achieved  19 and maintained for a longer period of time  20 with the 12-milligram versus the 6-milligram  21 dose.  22 In addition, when you look at the</p>

114	<p>1 clinical efficacy results, the consistency of  2 the 12-milligram dose seems to beat out the  3 6-milligram dose pretty much at all time  4 points. And let's just show you an example  5 of this.</p> <p>6 We're going to look here at the  7 studies, the initial trials, 313, 308, 302.  8 And the reason I'm focusing on that is  9 because those are the studies where in fact  10 there were two doses. As you've correctly  11 pointed out, there was only one dose in 314,  12 and there was a reason for that. We felt  13 that that was the appropriate dose. Here,  14 what you see is the hazard ratios for the key  15 endpoints:</p> <p>16 GI-2 ready for discharge and  17 discharge order written for the 6-milligram  18 dose. Now, let's bring on the 12-milligram  19 dose. And what you can see is that in each  20 instance, there is a somewhat more robust  21 response with the 12-milligram group as  22 compared to the 6-milligram group.</p>	116	<p>1 standpoint, what is the property that  2 determines the relative central versus  3 peripheral action of this opioid -- this  4 selectivity? Because, is there any potential  5 agonist effect that may relate to the issue  6 of fractures or falls, et cetera, or other  7 potential complications? So is there any  8 central effect, and what determines the  9 difference in central versus peripheral?</p> <p>10 DR. JACKSON: I'll give you the answer  11 as best I understand it from my limited  12 clinician's perspective. If we need more, we'll  13 ask one of our chemistry colleagues to come up.  14 But it is based on the physical-chemical  15 behavior of the molecule. It does not cross  16 membranes well. It is low in variable  17 absorption from the GI tract. And the parent  18 compound, therefore, doesn't get into the  19 blood -- into the CNS.</p> <p>20 DR. LINCOFF: Doesn't get into the  21 blood or doesn't get into the CNS?  22 DR. JACKSON: Doesn't get into the</p>
115	<p>1 So when you combine the PK profile  2 of 12 versus 6, the efficacy profile, the  3 safety profile which Dr. Jackson has shown  4 you is comparable. And you take into  5 consideration that for this condition, we  6 don't have the ability to titrate. There's  7 no time to titrate. We want to be sure that  8 that dose that we choose is the right dose  9 for the largest number of patients possible.</p> <p>10 When you combine all of that  11 collectively, that provides what we believe  12 is support for the 12-milligram dose. And I  13 think certainly we feel that that was borne  14 out in the results from the 314 study in  15 bowel resection only.</p> <p>16 DR. BUCHMAN: Dr. Lincoff?  17 DR. LINCOFF: I have two types of  18 questions, one just associated with some  19 pharmacokinetics and pharmacodynamics, which  20 I'll ask first, and then some regarding the  21 cardiovascular events.  22 First, from the pharmacodynamic</p>	117	<p>1 CNS. It gets into the blood. We have adequate  2 plasma levels to exceed the KI for the vast  3 majority of the time in most patients at a  4 12-milligram dose.</p> <p>5 DR. LINCOFF: And then focusing on the  6 cardiovascular adjudications that were done for  7 both the OBD studies and the postoperative ileus  8 studies, I understand that the Duke Clinical  9 Research Institute did the cardiovascular  10 adjudication for the postoperative ileus. And  11 when we compare the slides, I guess your Slide  12 CP-9 and CP-11, with adjudicated and  13 non-adjudicated, it's fairly straightforward to  14 look at the two, because the same endpoints are  15 used, and we also know a bit about the details  16 of how the DCR did they analysis.</p> <p>17 The concern that came up with the  18 cardiovascular, of course, came up with the  19 OBD. And I didn't see too much detail in  20 terms of what the constituency of this IDMC  21 was, or what constituted the IDMC. Who were  22 they? What was the process by which their</p>

118	<p>1 events were adjudicated?</p> <p>2       Because if you compare the slides</p> <p>3 of unadjudicated versus adjudicated there,</p> <p>4 the endpoints are classified differently. So</p> <p>5 among the questions who was on the committee,</p> <p>6 How were the -- which cases were chosen for</p> <p>7 adjudication and by what criteria, what</p> <p>8 source documentation they had? Can you</p> <p>9 provide some more details about that</p> <p>10 adjudication? Because that's really what</p> <p>11 brought the concern was that the OBD study.</p> <p>12       DR. JACKSON: You bet. I'm going to</p> <p>13 ask Dr. Camm. We're very fortunate to have the</p> <p>14 chairman of the IDMC here, and let him provide</p> <p>15 you that information.</p> <p>16       DR. CAMM: Good morning, Dr. Buchman.</p> <p>17 Good morning, ladies and gentlemen. My name is</p> <p>18 John Camm, and I'm from St. George's and the</p> <p>19 University of London in the U.K. I was the</p> <p>20 chair of the IDMC to which you refer. The other</p> <p>21 members of the IDMC were Tom Koch, a</p> <p>22 statistician; Jim Eisenach, a pain specialist;</p>	120	<p>1 were identified, and looked at all deaths.</p> <p>2 We used a standard criteria for definition of</p> <p>3 myocardial infarction and ischemic events,</p> <p>4 plus, of course, clinical judgment, because</p> <p>5 many of the cases did not have full</p> <p>6 documentation, although we had available to</p> <p>7 us all the source documentation that could be</p> <p>8 got back from the field.</p> <p>9       You'll recall that the GSK014 study</p> <p>10 did not start out seeking particularly to</p> <p>11 identify and evaluate cardiovascular safety</p> <p>12 as such. And therefore, there was no</p> <p>13 baseline electrocardiography lipid profiling,</p> <p>14 detailed cardiovascular history, and so on</p> <p>15 and so forth, nor was there for the first</p> <p>16 part, and as it turned out the most important</p> <p>17 part with regard to cardiovascular</p> <p>18 events -- the first part of GSK014 did not</p> <p>19 have any prospective data collection, so it</p> <p>20 all had to be trawled back from the field.</p> <p>21       So I hope that that answers your</p> <p>22 question of what constituted the committee</p>
119	<p>1 and two other cardiologists, Chris Cannon and</p> <p>2 Marc Pfeffer, both from Boston. We were</p> <p>3 constituted, as you probably know, about halfway</p> <p>4 through the ongoing 014 study, when it became</p> <p>5 apparent from the ongoing pharmacovigilance that</p> <p>6 there was an accumulating numerical excess of</p> <p>7 myocardial infarction appearing in association</p> <p>8 with treatment with alvimopan.</p> <p>9       Our mandate was to look at the</p> <p>10 opiate-induced bowel dysfunction development</p> <p>11 program for GSK and review the cardiovascular</p> <p>12 events in detail.</p> <p>13       So we chose prospectively to</p> <p>14 consider all deaths and all adverse events</p> <p>15 which were serious enough to require</p> <p>16 hospitalization. All of the latter were</p> <p>17 trawled by a third-party extractor to see if</p> <p>18 any of them had any cardiovascular element.</p> <p>19       We then as an adjudication group,</p> <p>20 which consisted just of the three</p> <p>21 cardiologists, looked at all of those</p> <p>22 cardiovascular serious adverse events which</p>	121	<p>1 and how the committee worked.</p> <p>2       DR. BUCHMAN: Dr. Richardson?</p> <p>3       DR. RICHARDSON: I have three</p> <p>4 questions. My first question is why is it that</p> <p>5 the studies using the GI-2 criteria seem to have</p> <p>6 a more favorable outcome for the drug than those</p> <p>7 using GI-3, when the only difference is dropping</p> <p>8 flatus as an endpoint? I mean, one would think</p> <p>9 that it should be no worse using GI-3 versus</p> <p>10 GI-2. So I'm wondering whether there are data,</p> <p>11 in fact, that combine both of these that we can</p> <p>12 see.</p> <p>13       Secondly, the second speaker</p> <p>14 indicated that there was a reduction in the</p> <p>15 incidence of nasogastric tube insertion by</p> <p>16 43 percent. And what were the actual</p> <p>17 percentages of those events in the placebo</p> <p>18 and drug treatment group?</p> <p>19       And I guess I'd like to get back to</p> <p>20 that question again on cardiovascular events.</p> <p>21 It seemed to me that from one of the slides,</p> <p>22 there was an excess number of patients I</p>

<p style="text-align: right;">122</p> <p>1 think in the OBD group that had arrhythmias.  2 And could you comment on that?  3 DR. JACKSON: All right. Thank you.  4 In terms of the first two parts of your question  5 on GI-2 versus GI-3 and the actual percentage of  6 nasogastric tube insertions, I'm going to ask  7 Dr. Techner to respond.  8 DR. TECHNER: There's one key  9 difference between GI-2 and GI-3, and that is  10 flatus. And I think certainly as clinicians, we  11 all know that the accurate reporting and  12 recording of that endpoint is very challenging.  13 And so certainly what we found in the data is a  14 lot of variability in that endpoint. Certainly  15 when patients are sleeping, whether or not they  16 feel comfortable reporting it to their  17 physician, I think it's a combination of factors  18 that contribute to that variability as opposed  19 to a bowel movement.  20 So number one, we feel, and I  21 believe FDA agrees, that GI-2 is the more  22 relevant endpoint and the more objective</p>	<p style="text-align: right;">124</p> <p>1 and 302, where GI-3 was the primary endpoint.  2 I think you can see here that certainly in  3 314, both GI-3 and GI-2 were statistically  4 significant; same in 313; close in 308, and  5 this may be due to the rule for adjusting for  6 multiple comparisons here, but the hazard  7 ratio, if you look at it itself -- and  8 competence interval could be considered  9 statistically significant if we didn't have  10 that little adjustment for multiple  11 comparisons; and 302, again, trending in the  12 right direction.  13 So I think you're correct in saying  14 it can't be that much worse. We agree, it  15 wasn't that much worse. However, in  16 evaluating the impact of alvimopan in this  17 population, we feel that GI-2 is the more  18 consistent and more appropriate because it  19 eliminates that variability of flatus.  20 Your second question -- I'm sorry,  21 I cannot -- ah, yes. May I have my core  22 slide, please? So here's the actual</p>
<p style="text-align: right;">123</p> <p>1 endpoint in measuring the treatment effect on  2 GI recovery.  3 DR. RICHARDSON: But GI-3 also  4 included bowel movement.  5 DR. TECHNER: Yes, it did.  6 DR. RICHARDSON: Right. So GI-3 can't  7 be worse than GI-2.  8 DR. TECHNER: Well, it's --  9 DR. RICHARDSON: You don't have to  10 satisfy all three requirements.  11 DR. TECHNER: For GI-3, it's whichever  12 occurred first.  13 DR. RICHARDSON: Correct.  14 DR. TECHNER: Right. And the  15 variability in reporting is how many times it  16 occurred first, how many times it occurred last,  17 et cetera. Whereas bowel movement seems to be  18 very consistent across the board. However,  19 let's look at the data.  20 And what I'm showing here is  21 Study 314, where the primary endpoint was  22 GI-2, and then the initial trials, 313, 308,</p>	<p style="text-align: right;">125</p> <p>1 percentage, about 11-1/2 percent of the  2 placebo patients had an NG tube inserted  3 postoperatively, versus approximately  4 7 percent of the Entereg 12-milligram  5 patients.  6 DR. RICHARDSON: Now, this is postop  7 insertion or reinsertion, the tube has come out  8 and having to have it put back in?  9 DR. TECHNER: It's postoperative  10 insertion. In other words, the patients were  11 required to have their NG tube removed by the  12 morning of Postoperative Day 1. In the vast  13 majority of cases, that did occur. If the NG  14 tube had to be inserted after that, reinserted,  15 that's what's counted here. Okay? So if they  16 had an NG tube or an OG tube during the case and  17 it was pulled, that was fine within the time  18 frame. If it was then inserted once again,  19 that's what makes up these percentages.  20 Does that clarify it for you?  21 DR. RICHARDSON: Right.  22 DR. BUCHMAN: It was announced,</p>

126	<p>1 though, that you had a 43 percent decrease in  2 the number of reinsertions of the NG tube. I  3 don't see where that 43 percent comes from.  4 DR. TECHNER: It's the relative  5 difference between 11-1/2 percent and  6 6.6 percent.  7 DR. BUCHMAN: I'm going to ask  8 actually a follow-up question on the NG tubes.  9 We've known for over 15 years, based on studies  10 with feeding jejunostomies, that patients could  11 be fed as early as even in the recovery room  12 following small bowel resections. So my  13 question is, what was the rush to remove the NG  14 tube? And why wasn't it actually placed in the  15 duodenum, for example, and perhaps the second  16 dose of medication, or the first  17 postoperatively, administered via the  18 nasogastric tube, and if the medication actually  19 has any effect on the stomach, which is actually  20 the major problem in terms of trying to feed  21 patients postoperatively and not the small  22 intestine?</p>	128	<p>1 tube. So rather than leaving it or placing  2 it in the duodenum until the morning after  3 surgery, we can simply avoid it altogether.  4 So the rationale for getting it out as soon  5 as possible, if it's placed, is the correct  6 one, and perhaps not even use it at all. And  7 then patients can get diet or liquids  8 immediately after surgery. And that's why  9 when you give this medication orally and know  10 now that it works well orally, it's obviously  11 beneficial to be able to do it in that  12 manner.  13 DR. BUCHMAN: Does the drug have any  14 effects on the stomach or gastric endthing (?) I  15 should say?  16 DR. TECHNER: We have, as you I  17 believe saw in your briefing document, done a  18 number of studies in order to try and understand  19 the pharmacokinetic-pharmacodynamic relationship  20 and the effect of this drug on GI transit time.  21 What we have found in all of those studies is  22 although alvimopan has an impact on both large</p>
127	<p>1 DR. TECHNER: I'm going to ask  2 Dr. Delaney to help answer that question with  3 respect to placement of the NG tube. While he's  4 making his way up here, certainly we, during the  5 trials, as you know, did not allow the use  6 of -- insertion of Entereg or placebo through  7 the NG tube if it was in place. There are  8 multiple reasons for that. As you know, that  9 can be fraught with potential complications, and  10 it's difficult to tell whether or not the  11 patient actually received the dose. So that was  12 not permitted within the trials.  13 As far as the second part of your  14 question, Dr. Delaney, could you respond,  15 please?  16 DR. DELANEY: Thank you, Lee.  17 Dr. Buchman, ladies and gentlemen, I'm Conor  18 Delaney from Case Western Reserve University.  19 You're quite correct that nowadays,  20 we do know that we can feed people early.  21 What we also know nowadays is that you  22 actually don't even require a nasogastric</p>	129	<p>1 bowel and small bowel transit, we have not seen  2 a clear response with respect to its effect on  3 GI transit time. So we have clear responses in  4 alvimopan being able to reverse the inhibition  5 of small bowel and large bowel motility, but we  6 don't have, at this point, clear data on how it  7 impacts gastric motility.  8 DR. BUCHMAN: So do you think that the  9 postoperative effect could be mediated solely by  10 the one preoperative dose, because  11 postoperatively, you've got doses -- a multiple  12 dose of medication sitting in the stomach and  13 not getting actually out of the stomach to have  14 a topical effect on the small bowel?  15 And would you, therefore,  16 potentially recommend perhaps only a  17 preoperative dose rather than postoperative  18 dosing, and has that been evaluated?  19 DR. TECHNER: The second part of your  20 question, the answer is no, we have not  21 evaluated that.  22 The first part of the question is,</p>

<p style="text-align: right;">130</p> <p>1 I believe what we have to take into  2 consideration here is that these patients are  3 being exposed over a relatively short period  4 of time to a consistent level of opioid. And  5 as long as they're exposed, that opioid is  6 going to have an impact on bowel motility.  7 We certainly believe that it is important to  8 mitigate those effects by maintaining  9 coverage on the receptors as long as  10 exogenous opioid, particularly parenterally,  11 is being administered. So that is the reason  12 for the dosing regimen.  13 DR. BUCHMAN: Our last question is  14 going to be Dr. Krist. I know there's a lot of  15 burning questions from the rest of the  16 committee. We'll have additional time this  17 afternoon that we're going to allot for  18 additional questions for the sponsor.  19 Dr. Krist?  20 DR. KRIST: I just have two questions  21 and they're unrelated, and I apologize for that.  22 One is further clarification about</p>	<p style="text-align: right;">132</p> <p>1 that the findings here in these studies might  2 apply if released into other community and  3 other settings.  4 DR. JACKSON: Thank you. I appear to  5 have engendered some misunderstanding in terms  6 of those data. The observation in the POI  7 studies was primarily in the first 14 days  8 pretty extensive and out through 30 days if and  9 when it could be done. And you're absolutely  10 correct that the myocardial infarctions in  11 Study 014 occurred between 40 and about 115 days  12 or whatever it was, so there was no overlap.  13 The point we were trying to get at with those  14 curves was that the period during which POI and  15 its observations took place did not result in  16 any excess cardiovascular morbidity in the OBD  17 studies either.  18 Then in regard to the hospital  19 settings, Dr. Delaney, would you have  20 anything to add about that? Because it's  21 very interesting when we look at how long  22 patients are in hospital, you're absolutely</p>
<p style="text-align: right;">131</p> <p>1 cardiovascular events.  2 I heard a statement made that in  3 the POI studies, that patients were followed  4 for 90 percent of the time period of when the  5 cardiovascular events occurred in the OBD  6 studies. And what I just wanted was a  7 clarification. Because when I look at Slide  8 CS-7 on the time to cardiovascular events, it  9 looks to me in the 014 study like  10 cardiovascular events are occurring between  11 40 and 120 days. And what I heard was in the  12 POI studies, that patients were followed up  13 to two to four weeks after a procedure, so  14 that seemed inconsistent.  15 The second question I had is just I  16 wanted to hear a little bit about the  17 hospital settings where these studies were  18 conducted. My guess would be that these are  19 more academic settings. And I'm just  20 thinking about the external validity or  21 generalizability of the time to discharge in  22 other settings, and whether we could expect</p>	<p style="text-align: right;">133</p> <p>1 right, most of these were academic centers.  2 DR. DELANEY: Conor Delaney, Case  3 Western Reserve University. Actually, one of  4 the strengths of this data set is that it was  5 accrued over a large number of centers,  6 including private practice and smaller centers  7 as well as larger academic institutions. So I  8 think the data set particularly shows that it  9 probably is very generalizable throughout  10 multiple types of clinical practice.  11 So I hope that answers your  12 question.  13 DR. BUCHMAN: We're going to take a  14 break for 15 minutes. Please be back here  15 sharply.  16 For committee members, feel free to  17 talk about your kids or the weather, but  18 refrain from talking about any of the data  19 that's been presented so that we can get it  20 transcribed in the record. Thanks.  21 (Recess)  22 DR. BUCHMAN: We're going to get</p>

<p style="text-align: right;">134</p> <p>1 started now. The FDA's presentation is going to  2 start with Dr. Ruyi He, who is the medical team  3 leader of the Division of Gastrointestinal  4 Products, and he's going to speak on the FDA's  5 analysis of the efficacy data.</p> <p>6 DR. HE: Good morning. My name is  7 Ruyi He. I'm medical team leader in the  8 Division of GI.</p> <p>9 Today, I will present clinical  10 efficacy and a general safety evaluation for  11 alvimopan. My presentation will focus on  12 alvimopan and a proposed indication.</p> <p>13 I'll wait for a minute. Okay.</p> <p>14 My presentation will focus on  15 alvimopan and a proposed indication,  16 regulatory history, POI clinical program, POI  17 efficacy results, POI general safety results,  18 and OBD clinical program. Then I will turn  19 to Dr. Dannis for a special safety  20 evaluation. She will be followed by the  21 presentation of non-clinical evaluation and  22 risk management.</p>	<p style="text-align: right;">136</p> <p>1 Main regulatory history. The  2 sponsor submitted the initial IND in August  3 1998, and a fast-track designation was  4 granted for POI indication in February 2004,  5 because we did believe that POI is a serious  6 condition with no available therapy for POI  7 indication. The sponsor submitted the  8 original NDA in June 2004, and approval  9 action was taken in July 2005, because of  10 insufficient evidence for efficacy.</p> <p>11 In May 2006, the sponsor submitted  12 a complete response, a second review cycle  13 start. During this period, a serious  14 cardiovascular event was identified in an  15 ongoing OBD study. That is Study 014, as  16 mentioned in the sponsor's presentation. In  17 November 2006, the sponsor submitted -- in  18 November 2006, FDA issued a second approvable  19 action letter and requested the final  20 12-month safety funding and a risk management  21 plan for the potential cardiovascular adverse  22 event.</p>
<p style="text-align: right;">135</p> <p>1 Alvimopan is a new molecular  2 entity. It's a peripherally-acting  3 opioid-receptor antagonist. Alvimopan has a  4 low systemic oral bioavailability, only about  5 6 percent. Tmax is about 2 hours and a  6 half-life ranged from 4 to 17 hours. There  7 is one active metabolite.</p> <p>8 The sponsor's proposed indication  9 is acceleration of time to upper and lower GI  10 recovery following partial large and small  11 bowel resection surgery with primary  12 anastomosis. In other words, the indication  13 is management of POI, postoperative ileus.</p> <p>14 POI is a transient impairment of GI  15 function after surgery. It is characterized  16 by inability to tolerate liquids and solid  17 food, nausea and vomiting, and/or abdominal  18 pain. Complications include prolonged  19 hospitalization and delayed nutrition. No  20 product is currently approved for POI  21 indication in the U.S. Off-label therapies  22 include metoclopramide and erythromycin.</p>	<p style="text-align: right;">137</p> <p>1 In April 2007, FDA put the  2 alvimopan program on clinical hold because of  3 an additional two cardiovascular events,  4 neoplasms, and a bone fracture were  5 identified in OBD studies. In August 2007,  6 the sponsor submitted a second complete  7 response. Now we are in the third NDA review  8 cycle. Due date is February 10, 2008.</p> <p>9 For the POI clinical program, the  10 sponsor conducted six Phase III clinical  11 studies. All are randomized, double-blind,  12 placebo-controlled studies in patients  13 undergoing partial large or small bowel  14 resection, or total abdominal hysterectomy  15 surgery. Study 001 was conducted in Europe  16 and Australia. All other studies were  17 conducted in the U.S. and Canada. Patients  18 on chronic opioids were excluded from the  19 studies.</p> <p>20 Since efficacy was not demonstrated  21 in the total abdominal hysterectomy surgery  22 subgroup in the original NDA submission, the</p>

<p style="text-align: right;">138</p> <p>1 sponsor decided to narrow proposed indication  2 to the bowel resection surgery population  3 only. Study 306 is not included in the  4 efficacy evaluation because no bowel  5 resection patient was enrolled in that study.  6 Treatment. The initial dose was  7 given a half-hour to two hours prior to  8 surgery. Subsequent doses were giving  9 12-milligram PO, BID from Post-Surgery Day 1  10 until hospital discharged, or until  11 Post-Surgery Day 7. The maximum number of  12 doses is 15, and a study drug only given in  13 hospital.  14 Key endpoints. GI-3 is time from  15 end of surgery to time of recovery of both  16 upper and lower GI tract function. Recovery  17 of upper GI tract function is indicated by  18 toleration of solid food, and a recovery of  19 lower GI tract function is indicated by first  20 bowel movement or first flatus. GI-3 was the  21 primary endpoint for Studies 302, 308, 313,  22 and Study 001.</p>	<p style="text-align: right;">140</p> <p>1 evaluation: The 25th percentile, median, and  2 the 75th percentile.  3 From this table you can see that  4 the patient trial medical alvimopan group had  5 a median time to achieve GI-3, 4.4 to 13.4.  6 All were earlier than the patient did in the  7 placebo group: 4.4 for Study 001, 13.4 for  8 Study 308. At the 75th percentile, the  9 differences were larger, from 7.5 hours to 21  10 hours. Hazard ratios are between 1.3 and  11 1.49. Because two different doses,  12 6 milligrams and 12 milligrams, were tested,  13 a significant level for P value per protocol  14 was less than 0.025. In this way, you can  15 see that for the first full study, only  16 Study 313, which is highlighted in here in  17 yellow, reached protocol-specified  18 statistically significant levels.  19 Based on those results at the end  20 of the first review cycle, the agency issued  21 an approval letter and required additional  22 efficacy data prior to approval. Study 314</p>
<p style="text-align: right;">139</p> <p>1 GI-2 basically is the same as GI-3  2 except without the evaluation of flatus. And  3 GI-2 was the primary endpoint for Study 314.  4 I do agree with the sponsor that GI-2 may be  5 a more objective endpoint than GI-3 because  6 it is very difficult to objectively assess  7 flatus.  8 Both DOW and Ready are the  9 secondary endpoints for all the studies.  10 Ready is time from end of surgery to time  11 ready for hospital discharge, based solely on  12 recovery of GI function as defined by the  13 surgeon. DOW is time from end of surgery to  14 time discharged order is written.  15 Now let's move to the efficacy  16 results. This table summarizes efficacy  17 results of time to recovery of GI tract  18 function measured by GI-3. As I mentioned  19 before, GI-3 was the pre-specified primary  20 endpoint for the first full study on this  21 slide and a secondary endpoint for Study 314.  22 Three time points were selected for this</p>	<p style="text-align: right;">141</p> <p>1 was then submitted in the second review  2 cycle.  3 Now let's see GI-2. GI-2 was the  4 primary endpoint for Study 314 only, which is  5 highlighted in here in yellow. From this  6 table, you can see that a patient in the  7 12-milligram alvimopan group had a median  8 time to achieve GI-2 -- 4.4 hours to 21.7  9 hours earlier than the patient did in the  10 placebo group. At the 75th percentile, the  11 differences were larger, from 18.7 hours to  12 28.9 hours. Hazard ratios are between 1.3  13 and 1.63. For Study 314, P value was less  14 than 0.001 and it is statistically  15 significant.  16 This table summarizes the results  17 for Ready, time from end of surgery to time  18 ready for hospital discharge. Ready was one  19 of the secondary endpoints for all studies.  20 From this table, you can see that the patient  21 in the alvimopan group had a median time to  22 achieve Ready 8 hours to 17.3 hours earlier</p>

<p style="text-align: right;">142</p> <p>1 than the patient did in the placebo group.  2 Hazard ratios listed here are between 1.1 and  3 1.54.  4 This table summarizes the  5 (inaudible) time to discharge order written,  6 DOW, in days. DOW was one of the secondary  7 endpoints for all studies. From this table,  8 you can see that Study 001, which was  9 conducted in Europe and highlighted here in  10 yellow, shows no difference between the two  11 groups.  12 However, for other (inaudible)  13 American studies, a patient in the alvimopan  14 group had a median time to achieve DOW .3 to  15 .8 days earlier than the patient did in the  16 placebo group.  17 At the 75th percentile, the  18 differences were larger, about one day early  19 shown here. From this column, you can see  20 that in all four North American studies, DOW  21 was consistently between six and seven.  22 However, in the Study 001, DOW was 11 days.</p>	<p style="text-align: right;">144</p> <p>1 hospital stay by roughly 1 day in the U.S.  2 The questions are: What is the minimum  3 acceptable efficacy difference for recovery  4 of GI function measured by GI-2 or GI-3 for  5 alvimopan relative to placebo? Do you  6 consider the efficacy results from the POI  7 studies which I present here today to be  8 clinically meaningful? Discussion will help  9 us to do benefit-risk assessment not only for  10 this drug, but also for other drugs with  11 similar indications.  12 Now let's move to general safety  13 evaluation in the POI population. A total of  14 4,000 patients are included in the POI safety  15 database. That includes 2,000 patients  16 received alvimopan.  17 This table summarizes demographic  18 data for overall POI population. Mean age  19 was 57 to 58 years old, and 35 percent of  20 them were patients 65 years old or older.  21 The majority, 85 percent, were Caucasian in  22 all groups. More female patients were</p>
<p style="text-align: right;">143</p> <p>1 When compared to the U.S. study, Study 001  2 has a similar time to recovery of GI tract  3 function measured by GI-3 and GI-2, but a  4 different time to discharge order written,  5 DOW, suggesting different clinical practices  6 in Europe with regard to hospital discharge.  7 In Europe, discharge may be delayed beyond GI  8 recovery.  9 This table summarizes results of  10 mean length of hospital stay by study. Three  11 of four North American studies indicate that  12 the hospital stay was one day shorter for  13 patients in the 12-milligram group than  14 patients in the placebo group, shown in here.  15 Again, Study 001 has a longer hospital stay  16 than the U.S. studies. Nine days versus five  17 to six days.  18 Efficacy summary in POI population.  19 Efficacy data demonstrated that there was  20 acceleration of recovery of upper and lower  21 GI tract function by roughly about 20 hours  22 measured by GI-2, and a reduced length of</p>	<p style="text-align: right;">145</p> <p>1 enrolled in the POI program, because  2 initially, the target population included  3 patients with hysterectomy surgery. For the  4 patients with bowel resection surgery only,  5 male and female were similarly represented in  6 each group, and equally distributed between  7 the treatment groups.  8 In the POI population, mortality  9 was the same in the placebo and in the  10 alvimopan group. So here, 0.5 percent, and  11 at 0.7 percent in the placebo.  12 Non-fatal serious adverse events  13 were numerically lower in the alvimopan group  14 compared to the placebo group -- 12 percent,  15 12 percent versus 18 percent. This was  16 mainly due to fewer postoperative ileus and  17 small bowel obstruction in the alvimopan  18 groups. So in here, 2 percent, 2 percent  19 versus 6 percent.  20 This slide summarizes the results  21 for discontinuations due to adverse events.  22 The data indicates that a proportion of</p>

<p style="text-align: right;">146</p> <p>1 patients with discontinuations due to adverse  2 events was numerically lower in the alvimopan  3 groups compared to the placebo group,  4 8 percent versus 12 percent. This was also  5 mainly due to fewer GI adverse events in the  6 alvimopan groups. Fewer GI adverse events in  7 the alvimopan groups may indeed support  8 efficacy claim of acceleration of GI tract  9 recovery.</p> <p>10 For treatment-emergent events in  11 the bowel resection population, there was  12 either a smaller or similar proportion of  13 patients with treatment-emergent events in  14 the alvimopan groups compared to that in the  15 placebo group, as shown in this slide:  16 43 percent, 49 percent, 12 percent,  17 21 percent, 12, 14, 8, 9.</p> <p>18 General safety summary in the POI  19 population. Similar or lower incidences of  20 death, nonfatal SAEs, discontinuations due to  21 AEs, and treatment-emergent events were  22 identified in the alvimopan group in</p>	<p style="text-align: right;">148</p> <p>1 difference is that it's used in the hospital  2 only for POI indication, but in the OBD  3 program, it's mainly used for outpatient  4 therapy.</p> <p>5 Before I turn to Dr. Dannis for a  6 special safety evaluation, I want to say  7 thanks to everyone in the review team,  8 especially my thanks to Eric Brodsky. Eric  9 was the primary medical reviewer for this  10 submission, and did excellent clinical  11 evaluation. Thanks.</p> <p>12 Now is Dr. Dannis.</p> <p>13 DR. DANNIS: Good morning. I'm going  14 to be discussing three special safety issues:  15 Serious cardiovascular events, neoplasms, and  16 fractures. Each of these issues was identified  17 as a possible safety problem in a year-long  18 safety study for opioid-induced bowel  19 dysfunction, or OBD, while alvimopan was under  20 review for the POI indication. Because of these  21 potential safety concerns, the studies for the  22 POI indication and the OBD indication were</p>
<p style="text-align: right;">147</p> <p>1 comparison with the placebo group in the POI  2 population.</p> <p>3 Now let's move to chronic  4 opioid-induced bowel dysfunction, OBD,  5 program. OBD is a chronic condition  6 characterized by decreased frequency of bowel  7 movement and associated symptoms. Patients  8 in the OBD studies were treated for chronic  9 pain with opioids for months or years instead  10 of days in the POI program. Although current  11 submission is only for POI indication,  12 imbalances in cardiovascular events,  13 neoplasms, and bone fractures were identified  14 in the OBD clinical studies.</p> <p>15 This slide shows the difference in  16 dosing regimen in the POI and OBD studies.  17 In the OBD program, the dose was much  18 smaller: 0.5 milligram QD or BID, in  19 comparison with 12 milligrams BID in the POI  20 program. However, duration was longer, up to  21 a year in the OBD program, instead of up to  22 eight days in the POI program. Another</p>	<p style="text-align: right;">149</p> <p>1 reanalyzed, concentrating on each problem.  2 Thus, I'll be discussing each issue as it  3 relates to both indications, POI and OBD.</p> <p>4 First, cardiovascular safety in the  5 POI program. The cardiovascular risk factors  6 in the worldwide POI population were  7 well-balanced between treatment groups. The  8 average age was about 57 for both groups, and  9 each had an equal percentage of patients with  10 diabetes, hypertension, and obesity. Smokers  11 made up about 9 percent of both groups.</p> <p>12 Here, we have the total number of  13 patients who had serious cardiovascular  14 events in the whole POI population. As you  15 can see, patients in the alvimopan treatment  16 group had a similar number of cardiovascular  17 events as compared to patients in the placebo  18 group. Cardiovascular death as well as  19 all-cause death were essentially balanced  20 between treatment groups.</p> <p>21 The total cardiovascular events  22 which occurred were separated into ischemic</p>

150	<p>1 events and other serious cardiovascular 2 events. Ischemic events were defined as 3 myocardial infarction, cerebral vascular 4 accident, and unstable angina. Other serious 5 cardiovascular events included congestive 6 heart failure, serious arrhythmia, cardiac 7 arrest, and non-ischemic cardiovascular 8 death.</p> <p>9       Once again, there does not seem to 10 be any difference between treatment groups in 11 the percentage of these events. Multiple 12 independent analyses of the specific 13 cardiovascular events were carried out. And 14 although the interpretation of certain events 15 was different, the overall assessment was the 16 same: There were no apparent differences in 17 the occurrence of serious cardiovascular 18 events in the alvimopan group as compared to 19 the placebo group. The time-to-event 20 analysis shows that the occurrence of CV 21 events are distributed fairly uniformly over 22 time for both groups.</p>	152	<p>1 patients who completed the study per the 2 sponsor's protocol had no follow-up after 3 discharge.</p> <p>4       In the POI program, a patient was 5 considered to have completed the study if all 6 protocol-specified in-hospital assessments 7 were completed. Therefore, there were some 8 limitations of the POI study designs.</p> <p>9       As I mentioned, follow-up was by 10 phone call only. Important safety endpoints 11 such as 30-day and 60-day morbidity and 12 mortality were not collected. Cardiovascular 13 events were not prospectively defined nor 14 consistently assessed post-exposure, and the 15 fact that the data wasn't there doesn't 16 really imply that there were no serious 17 cardiovascular events that occurred. In 18 conclusion, the POI studies were not 19 adequately designed to properly assess 20 cardiovascular risks.</p> <p>21       Next, we'll move on to 22 cardiovascular safety in the OBD population.</p>
151	<p>1       This table describes what happened 2 to the patients after they left the hospital. 3 In most all of the POI studies, the 4 protocol-defined hospital follow-up was by 5 telephone call. As you can see here, the 6 majority of patients had their last contact 7 by telephone at between 6 and 14 days. Some 8 had phone follow-up one to five days after 9 discharge. Few patients had any follow-up 10 beyond two weeks.</p> <p>11       For the patients who did have an 12 investigator follow-up visit, most were also 13 seen 6 to 14 days later. This visit occurred 14 in 7 percent of the placebo patients and 15 14 percent of alvimopan patients. Less than 16 1 percent of patients had a 17 protocol-specified investigator visit more 18 than two weeks after discharge.</p> <p>19       In addition, there were 580 20 patients who discontinued treatment for any 21 reason. It's unclear how many of these 22 patients were lost to follow-up. Also, 257</p>	153	<p>1 The major OBD trials were divided into two 2 categories: Studies with patients taking 3 opiates for non-cancer pain and studies with 4 patients taking opiates for cancer pain.</p> <p>5       Here's a table of all of the 6 relevant Phase II and Phase III studies. In 7 white are all the non-cancer studies except 8 Study 14, which is in red. As I mentioned, 9 this was the large, year-long, non-cancer 10 study which had some potential safety issues.</p> <p>11       In green are the cancer pain 12 studies. Here, we have the total number of 13 patients who had serious cardiovascular 14 events in the non-cancer OBD population. 15 More than twice as many patients who took 16 alvimopan had a serious cardiovascular event 17 as compared to patients who took placebo.</p> <p>18       Here, once again, the events were 19 divided into ischemic and non-ischemic 20 events. Both of these show an imbalance 21 between treatment groups.</p> <p>22       Now we look at Study 14 alone.</p>

<p style="text-align: right;">154</p> <p>1 2.6 percent of all the alvimopan patients had  2 a serious cardiovascular event, yet the  3 placebo patients had no events. Of note here  4 is the lower confidence bound of about a  5 twofold risk increase for CV events.  6 Here, the events are broken down  7 into ischemic and non-ischemic events.  8 Still, large differences between treatment  9 groups exist. Of note is that 7 of the 11  10 ischemic events in Study 14 were MIs.  11 Now we look at the entire OBD  12 population, non-cancer plus cancer studies.  13 There are continued differences between  14 treatment groups in the total cardiovascular  15 events, cardiovascular deaths, and now also  16 in all-cause death. Broken down into  17 ischemic and non-ischemic events, the  18 differences persist, with more events  19 occurring in the alvimopan group.  20 This table presents the time to all  21 CV events by varying intervals. As can be  22 seen, most of the events in the alvimopan</p>	<p style="text-align: right;">156</p> <p>1 patient demographics or underlying CV risk  2 factors within Study 14. But the duration of  3 most of the other OBD studies was from 3 to  4 12 weeks, and for Study 14, it was 12 months.  5 In summary, there is a numeric  6 imbalance of the serious cardiovascular  7 events seen in the pooled analyses of OBD  8 studies, and most strikingly in Study 14  9 alone. These findings are not predicted by  10 the preclinical findings, as my colleague  11 will discuss in the next presentation. This  12 may suggest that chronic alvimopan use can  13 increase risk of serious CV events in the OBD  14 population. However, the implications for  15 the short-term POI use are unclear.  16 Now we move on to the next topic,  17 neoplasms. And first, neoplasms in the POI  18 population. There were several different  19 types of neoplasms identified. No particular  20 kind of malignancy seemed to predominate. As  21 mentioned, these studies were of short  22 duration with mostly phone follow-up, which</p>
<p style="text-align: right;">155</p> <p>1 group occur between 31 and 180 days. This  2 table presents the time to all ischemic CV  3 events by varying intervals. Again, most of  4 the events in the alvimopan group occur  5 between 31 and 180 days.  6 Here is the time to CV event  7 analysis. The risk appears constant over the  8 entire time period even though the majority  9 of CV events in the alvimopan group occur  10 between 31 and 180 days. The plot also  11 suggests increased risks with increased  12 exposure to alvimopan. Note that the number  13 of patients in the risk set drops off around  14 Day 42 and again at Day 84 due to the  15 completion of 6-week and 12-week studies.  16 What remain are those patients in the  17 long-term Study 14.  18 In looking for reasons to explain  19 the imbalance, there were no differences in  20 patient demographics or underlying CV risk  21 factors between Study 14 and the other OBD  22 trials, and there were no differences in</p>	<p style="text-align: right;">157</p> <p>1 usually didn't exceed two weeks. Both  2 treatment groups appeared balanced for  3 neoplasia events.  4 There isn't much to say about  5 neoplasms in the POI studies, but to  6 summarize, the percent of neoplasms reported  7 in each treatment group appears to be  8 similar. The POI study design doesn't allow  9 for any real conclusions to be drawn.  10 For OBD, I'm going to discuss  11 neoplasms in the non-cancer studies, and then  12 the neoplasm deaths in the cancer studies.  13 In general, the incidence of neoplasia was  14 low across all non-cancer OBD studies.  15 But numerical imbalances were  16 observed between treatment groups in the  17 number of total neoplasms. Alvimopan-treated  18 patients had a higher percentage of neoplasms  19 than those patients who received placebo.  20 Similarly, when the total number was divided  21 into malignant and benign neoplasms, in both  22 categories, the same imbalance persisted.</p>

158	<p>1 The alvimopan treatment group had a higher 2 percent of neoplasms as compared to the 3 placebo group.</p> <p>4 Given that the original neoplasm 5 imbalance was reported from Study 14, this 6 study was again analyzed separately. Even 7 with an additional placebo case discovered 50 8 days after study completion, the relative 9 risk of all neoplasms was 2.5 in 10 alvimopan-treated subjects compared to 11 placebo-treated subjects.</p> <p>12 The time to malignant neoplasm for 13 alvimopan patients varied from less than 14 1 week to greater than 10 months. Six cases 15 occurred in two months or less. Many of the 16 others occurred after six months, all of 17 these in Study 14. All except one of the 18 benign neoplasms occurred in Study 14. The 19 majority occurred after six months of 20 treatment.</p> <p>21 There were three neoplasms reported 22 in the placebo patients. These cases</p>	160	<p>1 time-to-event analysis is once again 2 difficult to interpret. As time increases 3 there are so few patients left in the study, 4 especially in the placebo group.</p> <p>5 There were imbalances noticed 6 between treatment groups in the percent of 7 certain malignancies. For example, in 8 Study 008, more subjects with head and neck 9 cancers received alvimopan than placebo. 10 However, the deaths were almost entirely in 11 GYN, GY, and breast cancers. In contrast, in 12 Study 684, more subjects with non-small cell 13 lung cancer received alvimopan than placebo 14 and here more deaths did occur in patients 15 with non-small cell lung cancer.</p> <p>16 There were also imbalances noticed 17 in the baseline performance status between 18 treatment groups. In Study 008, Karnofsky 19 Performance scores appeared balanced between 20 treatment groups. However, in Study 684, 21 there was a higher percentage of patients 22 with lower Karnofsky Performance scores in</p>
159	<p>1 occurred from about 6 weeks to greater than 2 52 weeks. The time-to-event analysis is 3 difficult to interpret with such a small 4 number of events, but it suggests that 5 increased exposure to alvimopan may increase 6 neoplasm events.</p> <p>7 The most common neoplasms reported 8 in the non-cancer studies were squamous cell 9 carcinoma, breast cancer, and lung cancer.</p> <p>10 Now we move on to the OBD studies 11 in patients with cancer. Study 008 and the 12 Extension Study 684 were the two main OBD 13 studies in cancer-related pain.</p> <p>14 While reviewing the neoplasms in 15 these studies, an imbalance between treatment 16 groups and the death rates was noticed. 17 There were 10 deaths in Study 008; 9 occurred 18 in the alvimopan group. In Study 684 there 19 were 13 deaths; 11 occurred in the alvimopan 20 group. Combining these studies, 13 percent 21 of the alvimopan group died as opposed to 22 4 percent of the placebo group. The</p>	161	<p>1 the alvimopan group as compared to the 2 placebo group: 42 percent versus 13 percent, 3 respectively.</p> <p>4 The demographic characteristics and 5 extent of metastatic disease were similar 6 between the Study 008 and Study 684 7 populations, and were balanced between 8 treatment groups within each study.</p> <p>9 In summary, for the non-cancer OBD 10 population, alvimopan-treated patients had a 11 higher incidence of neoplasia events as 12 compared to placebo. These results were 13 possibly driven by the imbalance in neoplasia 14 events seen in the only long-term safety 15 study for non-cancer patients. There's no 16 apparent reason for the observed imbalance 17 between treatment groups in this 18 placebo-controlled study.</p> <p>19 In summary, for the cancer OBD 20 population, there was a large discrepancy 21 seen in the death rates between treatment 22 groups in Study 008 and Study 684. However,</p>

<p style="text-align: right;">162</p> <p>1 some differences in cancer etiology and  2 patient performance status did exist.  3 The final topic is fractures,  4 beginning with the POI population. Only one  5 patient with a fracture was identified. This  6 patient sustained multiple rib fractures  7 secondary to a syncopal event and fall after  8 a bowel resection surgery. No real  9 conclusions can be drawn from this one case.  10 Now, fractures in the OBD  11 population. When you look at the fracture  12 incidence in the entire OBD population,  13 non-cancer plus cancer studies, there wasn't  14 any difference between treatment groups.  15 However, again, when you look at Study 14  16 alone, the difference between treatment  17 groups is apparent. There was a 3.7 percent  18 fracture rate in alvimopan patients, versus a  19 1.1 percent rate in placebo patients.  20 This table describes the location  21 of all of the fractures. Interestingly, the  22 more typical osteoporotic-type fractures,</p>	<p style="text-align: right;">164</p> <p>1 of treatment and risk of bone fracture. But  2 given the small number of fractures, this  3 analysis is somewhat limited.  4 When adverse events were reviewed,  5 there did not seem to be an imbalance between  6 treatment groups for factors that might  7 increase fall risk, fractures such as  8 dizziness, syncope, gait instability, et  9 cetera. Of the subjects who reported  10 fractures, certain demographic  11 characteristics were imbalanced between  12 treatment groups.  13 The alvimopan group had a higher  14 percentage of women, more individuals aged 65  15 or older, and a higher average BMI. Baseline  16 demographics, except advanced age, were  17 well-balanced between treatment groups in  18 Study 14 as well as in the total OBD  19 population. Additionally, the mean opioid  20 daily dose was similar between treatment  21 groups.  22 In summary, for the OBD population</p>
<p style="text-align: right;">163</p> <p>1 such as hip and vertebral, were rarely seen.  2 The bones most frequently broken were the  3 ribs and extremities. The same fracture  4 locations were seen in Study 14, where the  5 majority of events occurred. More of the  6 fractures in the alvimopan group were in  7 women, but once again, these were not  8 osteoporotic fractures.  9 When we looked at time to fracture,  10 fracture rates were reasonably balanced  11 between treatment groups until about six  12 months. After this, most of the events  13 occurred in the alvimopan treatment group.  14 Although the causality for many of the  15 fracture cases was not determined, the  16 overwhelming majority of cases were secondary  17 to falls.  18 Here is the time-to-fracture  19 analysis only for Study 14. The majority of  20 fractures were reported after 12 weeks of  21 treatment. In the alvimopan group, there  22 appears to be a relationship between duration</p>	<p style="text-align: right;">165</p> <p>1 fractures were not the typical osteoporotic  2 fractures, such as hip and vertebral. The  3 patients with fractures in the alvimopan  4 group were more commonly women than in the  5 placebo group. More fractures were secondary  6 to falls, and confirmatory information was  7 often not available. The etiology for the  8 imbalance seen in fracture rates between  9 treatment groups, mainly in Study 14, is  10 unclear.  11 So, to summarize overall, what we  12 have is the largest long-term safety study of  13 alvimopan for the OBD indication showed  14 potential safety signals in three specific  15 areas: Serious cardiovascular events,  16 neoplasms, and fractures. The POI studies  17 did not show any evidence of these safety  18 signals. However, the follow-up of patients  19 was extremely limited.  20 Next we'll hear about the  21 preclinical findings.  22 MR. CHAKRABORTI: Good morning. I'll</p>

<p style="text-align: right;">166</p> <p>1 present the nonclinical studies and the results  2 of the nonclinical studies for alvimopan.  3 Alvimopan has been adequately  4 tested in a wide variety of nonclinical  5 studies at sufficiently high doses. These  6 studies include several in vitro and in vivo  7 pharmacology studies -- safety pharmacology  8 studies that examined the effects of  9 alvimopan on the central nervous system,  10 gastrointestinal system, cardiovascular  11 system, and renal system.  12 In addition to that, the  13 absorption, distribution, metabolism, and  14 excretion studies are also conducted in  15 several species, in rats and rabbits. The  16 acute, subacute, subchronic, and chronic  17 toxicology studies were also conducted in  18 mice, rats, and rabbits.  19 The genotoxic potential for  20 alvimopan and its active metabolite,  21 ADL 08-0011, was also tested in a complete  22 battery of genotoxicology studies. The</p>	<p style="text-align: right;">168</p> <p>1 and conscious dogs, alvimopan did not produce  2 any significant effect, including  3 prolongation of QT or any other effects on  4 ECG up to a dose of 2.5 milligrams per  5 kilogram, IV.  6 The toxicology studies, there is no  7 significant target organ in any of the  8 toxicology studies in any of the species  9 tested. There was no significant effect on  10 either bone, including the bone marrow, and  11 alvimopan did not produce any significant  12 toxicity in the heart in any of the  13 toxicology studies. The no observed adverse  14 effect level, or NOAEL, was identified in a  15 six-month chronic toxicity study in rats at  16 200 milligrams per kilograms per day. And  17 the value for dog was 100 milligrams per  18 kilograms per day in a six-month oral  19 toxicity study.  20 As I mentioned before, the  21 genotoxicity for alvimopan and its active  22 metabolite was tested in a complete battery</p>
<p style="text-align: right;">167</p> <p>1 carcinogenicity studies were conducted by  2 using two-year (inaudible) in mice and rats.  3 And lastly, the reproductive and  4 developmental toxicity of alvimopan was  5 tested in rats and rabbits.  6 Let me walk you through some of the  7 major findings from these nonclinical  8 studies. I'll first discuss the  9 cardiovascular safety pharmacology studies.  10 In hERG assay, alvimopan did not  11 show any significant inhibition of hERG  12 current up to 50 micromolar concentration.  13 In isolated canine or dog Purkinje fiber  14 experiment, there was no significant effect  15 on action potential duration or any other  16 parameters that were tested up to 100  17 micromolar concentration.  18 In rats, the cardiovascular effects  19 of alvimopan was tested up to 200 milligrams  20 per kilograms by oral route, and there was no  21 significant effect on any of the  22 cardiovascular parameters. In anesthetized</p>	<p style="text-align: right;">169</p> <p>1 of genotoxicity studies that includes Ames  2 test, mouse lymphoma assay, chromosomal  3 aberration test, and mouse micronucleus test.  4 In all these studies, alvimopan was negative.  5 The active metabolite was tested in  6 Ames assay, chromosomal aberration assay in  7 Chinese hamster ovary cells, and mouse  8 micronucleus test. And in all these tests,  9 this active metabolite was also negative.  10 Two-year oral carcinogenicity  11 studies were conducted in rats and in mice.  12 In rats, the doses were 100, 200, and 500  13 milligrams per kilograms per day. And in  14 mice, these doses were 100, 1,000, and 4,000  15 milligrams per kilograms per day.  16 These are the neoplastic findings  17 for the carcinogenicity study. I'll first  18 discuss the results on the mouse. There was  19 a statistically significant positive trend  20 and pairwise difference versus vehicle  21 control at the highest dose, which is 4,000  22 milligrams per kilogram in the combined</p>

<p style="text-align: right;">170</p> <p>1 incidences of fibroma, fibrosarcoma, and  2 sarcoma in the skin and subcutis only in the  3 female mice. In addition, there was a  4 statistically significant positive trend and  5 pairwise difference compared to the vehicle  6 control at the highest tested dose of 4,000  7 milligrams per kilograms per day in the  8 combined incidences of osteoma and  9 osteosarcoma in the bones in female mice.  10 Alvimopan was negative in the rat and did not  11 produce any significant tumor.  12 This table summarizes the  13 incidences of tumor in the female mice in the  14 two-year bioassay. The first column shows  15 the type of the organ and the second column  16 shows the tumor type, and then the dose  17 groups and the P value for the trend test.  18 As you can see for the bone, there  19 is combined incidences when osteoma and  20 osteosarcoma were combined. There were no  21 incidences in the vehicle control or the  22 low-dose, one incidence in the mid-dose, and</p>	<p style="text-align: right;">172</p> <p>1 preclude approval of alvimopan.  2 To summarize, the nonclinical  3 findings for alvimopan in cardiovascular  4 safety pharmacology studies or in other  5 safety pharmacology studies, there are no  6 notable effects. In toxicology studies,  7 there is no significant target organ of  8 toxicity. And in genetic toxicology studies,  9 alvimopan and its active metabolite was  10 negative. In carcinogenicity studies, it was  11 only positive in female mice. However, it  12 was negative in rat. And in reproductive  13 toxicology studies, alvimopan didn't show any  14 adverse effect on fertility and reproductive  15 performance in rats. And it is not  16 teratogenic in rats and rabbits.  17 I thank you everybody in the agency  18 for contributing to this project, and also  19 thank you all for your attention.  20 MS. WEAVER: I'm going to talk about  21 Risk Minimization Action Plans, or RiskMAPs.  22 I'll present some background about the content</p>
<p style="text-align: right;">171</p> <p>1 there were four incidences at the high dose.  2 And it was statistically significant, at the  3 level of P 0.025. If we look at the skin and  4 subcutis, when these tumors were combined,  5 fibroma, fibrosarcoma, and sarcoma, you see  6 there are five incidences of these tumors at  7 the high dose and none in control, low-, or  8 mid-dose, and it was also statistically  9 significant.  10 Now, these findings in the female  11 mice was observed about eight times the human  12 exposure at the recommended dose. These  13 tumor incidences were statistically  14 significant only in one sex. And there was  15 no statistically significant findings either  16 in the male mice or in the female rates, or  17 in other words, alvimopan was not a  18 transspecies or a transgender animal  19 carcinogen.  20 And the relevance of these findings  21 to human is unknown. And such type of tumor  22 findings in the female mice generally do not</p>	<p style="text-align: right;">173</p> <p>1 and use of RiskMAPs, and then I'll address what  2 the sponsor has proposed for alvimopan.  3 So what is a RiskMAP, a Risk  4 Minimization Action Plan? A RiskMAP is a  5 strategic safety program designed to meet  6 specific goals and objectives in minimizing  7 product risks. A RiskMAP employs one or more  8 RiskMAP tools to achieve the goals and  9 objectives of the RiskMAP. And RiskMAPs go  10 beyond the FDA-approved labeling.  11 So how do RiskMAPs work? There are  12 several strategies that are used within  13 RiskMAPs. Depending on the nature of the  14 product and the nature of the risk, one or  15 more of these strategies might be used.  16 The use of a product could be  17 limited to settings or patients with a good  18 risk-benefit profile, or to look at the  19 reverse of that, the use of the product could  20 be prevented in high-risk settings or  21 patients. The RiskMAP can encourage or  22 mandate safety-related monitoring. Therapy</p>

<p style="text-align: right;">174</p> <p>1 could be started in a closely monitored  2 setting if that's a period of high risk. A  3 RiskMAP can empower patients to participate  4 in medication-related decisions and safety  5 monitoring, with education or informed  6 consent. And RiskMAPs can educate health  7 care providers on safety-related issues and  8 monitoring.</p> <p>9       So what are the components of a  10 RiskMAP? A RiskMAP has goals and objectives.  11 And that's the desired end result or goal,  12 with intermediate steps, often stated in  13 terms of the health outcome we're trying to  14 avoid. For example, the goal in a clozapine  15 RiskMAP is to have no episodes of  16 agranulocytosis. An objective or  17 intermediate step to this goal is to perform  18 periodic white blood count monitoring in  19 patients receiving the product.</p> <p>20       A RiskMAP uses tools. These are  21 processes or systems beyond labeling to  22 achieve the goals and objectives. We</p>	<p style="text-align: right;">176</p> <p>1 delivered many different ways, including  2 "Dear Health Care Practitioner" letters;  3 training programs for health care  4 practitioners and patients; continuing  5 education; patient labeling, such as  6 medication guides and patient package  7 inserts; RiskMAP program guides; videos;  8 DVDs; and also limits in marketing or  9 promotion, such as no direct-to-consumer  10 advertising, or detailing only to certain  11 specialties.</p> <p>12       The next level of tool are reminder  13 or prompting systems. And the purpose of  14 reminder and prompting systems is to assist  15 health care providers in following  16 appropriate prescribing practices. Examples  17 of these systems include: limiting the supply  18 of product per prescription, such as  19 dispensing only a 30-day supply; limits on  20 the number of refills, or not allowing  21 refills at all; prescription expiration, such  22 as requiring a prescription to be filled</p>
<p style="text-align: right;">175</p> <p>1 characterize the tools into three different  2 categories: Education and outreach, reminder  3 or prompting systems, and finally, restricted  4 distribution, also called performance-linked  5 access systems.</p> <p>6       RiskMAPs also include an evaluation  7 component. We look at the health outcomes or  8 the surrogate of health outcomes to evaluate  9 the success of the RiskMAP, often numbers or  10 rates of an outcome or event. RiskMAPs can  11 also be evaluated for compliance with  12 important RiskMAP processes and procedures or  13 process outcomes. And RiskMAPs can be  14 evaluated by assessment of comprehension,  15 knowledge, or desired behavior, often through  16 surveys. And we often use that to assess the  17 educational component of a RiskMAP.</p> <p>18       Now, to turn to the RiskMAP tools,  19 targeted education and outreach is used to  20 communicate risks and appropriate safety  21 behaviors to health care practitioners and to  22 patients. Education and outreach can be</p>	<p style="text-align: right;">177</p> <p>1 within a certain period of time; specialized  2 packaging; packaging may require certain  3 warnings on the packaging; the packaging may  4 include a medication guide or patient package  5 insert; the specialized packaging may have a  6 pharmacist checklist; and there may be  7 limitations to the amount of product packaged  8 together.</p> <p>9       Another example of a reminder or  10 prompting system is prescriber or other  11 health care practitioner attestation of  12 conditions of safe use, and physician-patient  13 agreements as an informed consent.</p> <p>14       The highest level or most  15 restricted of the tool categories are  16 restricted distribution or performance-linked  17 access systems. The purpose of these systems  18 is to target the population and conditions of  19 use to those most likely to confer benefits,  20 and to minimize particular risks. This can  21 include restrictions on prescribing,  22 distribution, dispensing, and administering</p>

<p style="text-align: right;">178</p> <p>1 the product. Examples of these kinds of  2 systems are: Prescriptions only by specially  3 certified health care practitioners; product  4 dispensing that's limited to pharmacies or  5 health care practitioners that elect to be  6 specially certified; mandatory pharmacy  7 enrollment to dispense; mandatory enrollment  8 of infusion centers or hospitals to  9 administer; the drug could be dispensed or  10 administered only in certain health care  11 settings -- for example, the drug could be  12 administered in an acute care hospital;  13 product dispensing only to patients with  14 evidence or other documentation of safe use,  15 for example, required pregnancy testing or  16 required liver lab testing; and wholesaler  17 agreement to distribute product only to  18 registered entities.</p> <p>19 So when should a RiskMAP be  20 considered? Products with important benefits  21 should be considered for a RiskMAP if the  22 risks are serious, but preventable; if safe</p>	<p style="text-align: right;">180</p> <p>1 So the first question that we have  2 is whether the logic model holds. Do we  3 understand the risks? From Dr. Dannis'  4 presentation, you saw that the follow-up in  5 short-term trials might not have been  6 sufficient to ascertain cardiovascular and  7 other events that might have occurred outside  8 the period of observation. Additionally, we  9 note that the proposed daily dosage is 24  10 times higher than the dose that produced the  11 cardiovascular safety signal in longer term  12 testing.</p> <p>13 The RiskMAP outline submitted  14 proposes a RiskMAP comprised of these  15 elements: agreements with pharmaceutical  16 wholesalers to sell only to hospitals;  17 targeted education, sales, and promotion to  18 acute care hospitals; packaging that  19 specifies hospital use; and an alert system  20 for outpatient pharmacies to alert  21 pharmacists not to dispense on an outpatient  22 basis.</p>
<p style="text-align: right;">179</p> <p>1 and effective use requires specialized health  2 care skills or settings; when intervention is  3 needed to increase the benefits relative to  4 risks; and when the product is in a class of  5 products with similar risks that require a  6 RiskMAP.</p> <p>7 So now with that background, let's  8 turn to the RiskMAP proposed for alvimopan.  9 The proposed RiskMAP addresses cardiovascular  10 risk. So far, the sponsor has not made a  11 complete RiskMAP submission.</p> <p>12 An outline of a proposal has been  13 submitted, but the outline did not include  14 any goals, objectives, supporting documents,  15 detailed implementation plans, an evaluation  16 plan, metrics for evaluation, or the  17 frequency and content of RiskMAP reports to  18 the agency. The RiskMAP outline addresses  19 cardiovascular risk, and the logic of the  20 RiskMAP framework relies on the assumption  21 that cardiovascular risks will be minimized  22 by limiting use to inpatient settings.</p>	<p style="text-align: right;">181</p> <p>1 We are concerned that the current  2 proposal may not prevent longer term use or  3 outpatient use. We understand that  4 pharmaceutical wholesalers do not have a  5 definition of "acute care hospital," and they  6 may not be able to distinguish acute care  7 hospitals from surgery centers,  8 rehabilitation hospitals, or nursing homes,  9 for example.</p> <p>10 Many hospitals dispense for  11 outpatients. Physicians may want patients to  12 finish a course of therapy at home that  13 they've started in the hospital. Extended  14 inpatient stays are possible, and the product  15 could be used in that situation. And the  16 alert system for outpatient pharmacies is  17 available in 50 percent of pharmacies, and  18 the pharmacists can override the alert.</p> <p>19 We also note that the proposal does  20 not provide for the collection of medical  21 outcomes to determine if cardiovascular  22 events are indeed minimized. So we would not</p>

<p style="text-align: right;">182</p> <p>1 have that information to use to evaluate the 2 success of the RiskMAP. 3 To address some of the concerns I 4 showed you on the last slide, we have some 5 thoughts on tool selection that may address 6 some of them. We think that hospitals may 7 require more support for the safe use of the 8 product, and it might be useful to have 9 hospitals register and attest that they have 10 a safe-use protocol in place. And we have 11 experience with a RiskMAP for dofetilide that 12 uses attestation of a safe-use protocol. 13 Also, because of the problems we 14 see with wholesalers making the decision on 15 who can buy the product, we would suggest 16 that the sponsor retain control of who 17 purchases it. And we do have an example of 18 that as well in which the product is ordered 19 through the wholesaler, but then okayed and 20 shipped through the sponsor. 21 So our conclusions about the 22 proposed alvimopan RiskMAP: we need much more</p>	<p style="text-align: right;">184</p> <p>1 was used? There is publicly submitted data 2 that would suggest an improvement in efficacy 3 over the 3-milligram dose, but I'm still 4 curious as to why the 12-milligram dose was 5 chosen. And can you shed some light on the 6 agency's evaluation of the efficacy 7 difference? 8 DR. HE: So I answer again here or I 9 should go there? I can stay here? Okay. 10 You are right, we do have a concern 11 which dose is the best dose for this 12 product -- for this program POI indication. 13 As you indicated, in the early study, they do 14 study several different doses, 3-milligram, 15 6-milligram, and 12-milligram. In my 16 presentation, I did not show the data for 17 6 milligrams, but I did include those data in 18 my background package. 19 In the initial submission, we have 20 a lot of discussion about which dose is the 21 best dose. Some studies do show 6 milligrams 22 is better than 12 milligrams. And we are</p>
<p style="text-align: right;">183</p> <p>1 detail about the goals, objectives, 2 implementation plans, evaluation plan, 3 metrics, and RiskMAP reporting to the agency. 4 We think that operational changes are needed 5 in the proposal that was submitted, and we 6 propose that the sponsor retain control over 7 the supply chain. And we think there may be 8 a need for a systematic program for hospitals 9 to prevent diversion to outpatient use and to 10 prevent longer term inpatient use. 11 Finally, even with these changes, 12 the RiskMAP framework is acceptable only if 13 short-term use is safe and if process 14 evaluation of the RiskMAP is sufficient, 15 because medical outcomes would not be 16 measured. 17 DR. BUCHMAN: Okay. We're going to 18 open the meeting up to questions for the 19 committee, to the FDA and FDA presenters. 20 Dr. He, in your analysis, did you 21 evaluate the efficacy difference between the 22 earlier studies where the 6-milligram dose</p>	<p style="text-align: right;">185</p> <p>1 concerned -- focused on the primary endpoint 2 and a second endpoint, like GI-2 and GI-3. 3 If you only focus on GI-3, you do find the 4 difference between 6 milligrams and 5 12 milligrams, and some data indicated that 6 6 milligrams is better based on GI-3. But if 7 you're checking the endpoint for GI-2, in 8 that case you're limited evaluation for 9 flatus, and then you can see 12 milligrams 10 compared to 6 milligrams, maybe 12 milligrams 11 is better. That data I saw in my background 12 package. 13 Like I said before, GI-2 only 14 secondary endpoint for the first full 15 Study 302, 308, 313, and 001. But doing the 16 evaluation, we do recognize that the flatus 17 is a very difficult endpoint to objectively 18 assess, especially the method the sponsor 19 used to assess the flatus. You know, you 20 wake up the patient every two hours to ask do 21 you have a flatus. And in this way, if you 22 ask my personal opinion, I do consider the</p>

186	<p>1 GI-2 is a more objective endpoint.  2 And based on GI-2, I do feel  3 12 milligrams may be better dose for the  4 further study, although the data do not show  5 in that way. But I have no objection for the  6 sponsor to choose 12 milligrams at a further  7 study. That is Study 314; they only study  8 for 12 milligrams.  9 DR. BUCHMAN: With the idea of trying  10 to use the minimal effective dose, do you think  11 another study comparing 6 and 12 milligrams  12 would be necessary?  13 DR. HE: No. Probably -- I mean, if  14 you do more studies, it's better -- we try to  15 collect more data, but probably not necessary.  16 The reason is there are five studies. If you  17 include Study 306, a total of six studies. And  18 though they did not show a significant dose  19 response between 6 and 12, when you evaluate for  20 the safety scenario, you do not see  21 12 milligrams increase significantly for a  22 safety issue. Therefore, we do not have an</p>	188	<p>1 afternoon then. Let's see, who was next here?  2 Dr. Pasricha?  3 DR. PASRICHA: I have a question for  4 Dr. He, also, which might require the sponsor's  5 response as well. But just looking at the  6 efficacy data by median and 75th percentile, the  7 difference in the median is only -- looking at  8 DOW, discharge order written, which is perhaps  9 the most relevant parameter here, is only 0.3  10 days. And it's only when you get to the 75th  11 percentile that you have a day difference. So  12 is the interpretation correct then that the  13 effect of this drug is really only valuable in  14 the patients who are in the outliers, and it may  15 not be as effective or as valuable in the  16 majority of the patients or at least in the  17 first five days to respond?  18 And then I guess a follow-up to  19 that is, has either the sponsor or your group  20 looked at differences in the profiles of  21 patients, early responders versus the late  22 responders, to try and see if there's some</p>
187	<p>1 objection for the sponsor to choose which one  2 they will go to further study, because Study 314  3 was only studied for 12 milligrams, you know.  4 At this time point, we will focus on  5 12 milligrams.  6 DR. BUCHMAN: Dr. Rosing?  7 DR. ROSING: Yes. We've heard about  8 Study 014, and the sponsor and Dr. Dannis has  9 described the various characteristics and  10 cardiovascular risk factors, et cetera, in the  11 study. Unless I missed it, I haven't heard,  12 though, what drugs those patients were on or  13 those subjects were on in addition to the study  14 drug; in other words, anti-platelet drugs,  15 statins, diabetic treatment drugs, et cetera.  16 Is there any reason to believe, or was it  17 examined to see whether there was any skewing of  18 the use of those drugs in the placebo versus the  19 treatment groups?  20 DR. KORVICK: It might be appropriate  21 to ask that question to the sponsor.  22 DR. BUCHMAN: Let's save that for the</p>	189	<p>1 marker that we can look at to identify which  2 patients may best respond?  3 DR. HE: Yeah. You're definitely  4 right. When we did the efficacy evaluation,  5 initially we focused on the median. Right now,  6 during my presentation, I chose three different  7 time points: 25 percent, median, and 75  8 percent. I tried to give balanced data to show  9 you all of the data.  10 To answer your question, the  11 difference between median and the 75th  12 percentile, roughly only 1 day difference.  13 If you're looking for the time achieved for  14 the median, roughly about four days. And if  15 you're looking for the 75th percentile,  16 roughly about 5 days.  17 And because this indication is POI  18 post-surgery, it is very difficult to assess  19 the early responder. Most of the patients,  20 they take several days to recover GI  21 function, you know? If you don't give a  22 treatment, roughly five days. And if you try</p>

190	<p>1 to see the early time, like a 75th  2 percentile, it is very difficult, because  3 this disease -- the nature of the disease.  4 Therefore, we later on -- initially, we only  5 focus on median, but later on, I do agree to  6 looking at the data at the 75th percentile.  7 Because the total of the hospital  8 stay is seven days, and you want to evaluate  9 the totality of the data. Therefore, you  10 looking for the time point at 75th percentile  11 may be okay even at the later, after disease.  12 But there's still some -- the meaningful  13 difference between the two groups.  14 Therefore, either choose at Day 4 or Day 5, I  15 have no personal feeling. Either way is  16 okay.  17 DR. BUCHMAN: Dr. Proschan?  18 MR. PROSCHAN: Yeah. I think one of  19 the most important things that we have to do is  20 figure out whether 014, why is it different? Is  21 it a real difference?  22 And so I was looking at Dr. Dannis'</p>	192	<p>1 And the second question was -- oh,  2 there were no patients that were counted  3 twice for events, either for Study 008 and  4 684. Any patient that had an event only had  5 one and was counted once, especially in this  6 side because this side is the patient's  7 experience and serious cardiovascular events.  8 DR. BUCHMAN: Dr. Talamini?  9 DR. TALAMINI: So many surgeons have  10 used the admittedly off-label use of ketorolac  11 as a similar narcotic-sparing type of a  12 strategy. It looked like in only Study 001 that  13 was done overseas was that drug used. And I  14 wonder if there was enough data in there to  15 determine what the effect of that specific drug  16 was on the outcomes of that study.  17 DR. HE: Study 001 is a large study.  18 It includes more than 700 patients. They do  19 have some difference between the North American  20 study and Study 001, the European study. But I  21 do believe to evaluate the primary endpoint for  22 GI-2 or GI-3, Study 001 is still valid, which</p>
191	<p>1 Slide 18, and I wonder if we could put that  2 up. Yeah. So I'm trying to compare the  3 results for Study 014 with these results, and  4 these include 014, so I'm trying to subtract  5 out the 014. But the problem is, I think  6 that 008 and 684 involve the same patients.  7 Some of the patients are the same. And so it  8 looks like the N at the top isn't quite  9 right, because I think that N was obtained by  10 just adding the number of patients in those  11 two as if they were separate people.  12 And the other thing I worried about  13 with this slide, I want to make sure about  14 this, is that could someone have a CVD event  15 and then go into the extension study and have  16 another one and be counted twice? I can't  17 remember from the briefing document whether  18 there was anyone in that category.  19 DR. DANNIS: Is this on? Okay. To  20 answer your first question, the patients that  21 went from Study 008 to 684 were only counted  22 once, so that N should just be who was in 008.</p>	193	<p>1 should include those data for evaluation of GI  2 recovery.  3 But -- because, according to the  4 sponsor's presentation, you can see the  5 difference between the North American and  6 European clinical practice is different. And  7 therefore, I personally agree for evaluation,  8 DOW already for discharge or hospital stay,  9 Study 001 may not provide so much  10 information.  11 DR. KORVICK: As far as the  12 concomitant drugs, that's I think the second  13 time we've heard that question. I think that  14 maybe the sponsor might have some backup slides  15 to enlighten us later. Maybe this afternoon we  16 can come back to that. We're not prepared to  17 talk about that issue.  18 DR. BUCHMAN: As a follow-up question  19 to that, virtually all -- we don't know all, but  20 perhaps virtually all these patients were on a  21 PCA pump postoperatively. Postop ileus, by  22 definition, would be related to manipulation of</p>

194	<p>1 the bowel. Is the agency able or in need to  2 differentiate between postoperative ileus from a  3 bowel-related issue versus a narcotic-induced  4 ileus? And are we talking about two potential  5 different indications here?</p> <p>6 DR. KORVICK: I think that's an  7 interesting point that perhaps the group should  8 discuss in a broad way. We're looking for  9 feedback from you, and I think that we've seen  10 the data and what the sponsor's proposed, so  11 we'd be looking forward to that discussion later  12 this afternoon.</p> <p>13 DR. BUCHMAN: Dr. Kramer?</p> <p>14 DR. KRAMER: Yes, I had a question for  15 Dr. Dannis. A lot of the questions we'll have  16 to deal with this afternoon have to do with  17 assessing the clinical meaning of these results,  18 and for me, that ties both benefit and risk.  19 You have clearly pointed out that although there  20 wasn't a cardiovascular signal seen in the POI  21 studies, the follow-up was limited and the  22 extent to -- in fact, there were over 250</p>	196	<p>1 over time. Were the bowel resection studies  2 completed before the questions of cardiovascular  3 risks were known? And when these questions  4 surfaced, did the agency feel that these  5 patients needed to be re-consented?</p> <p>6 DR. HE: For your first question, yes,  7 during the end of the first review cycle, we did  8 not have identify any specific safety issues.  9 We issued an approval letter purely because of  10 the advocacy issue.</p> <p>11 Cardiovascular events were  12 identified after we issued the approval  13 letter, that is during the second review  14 cycle, after the sponsor submitted the second  15 NDA. During that period, we identified the  16 imbalance cardiovascular events during the  17 interim analysis for that 12-month safety  18 study. And that is why the study for the POI  19 program is not designed to capture those  20 kinds of events.</p> <p>21 DR. RICHARDSON: But what about the  22 question of re-consenting patients once that</p>
195	<p>1 patients that didn't have any follow-up after  2 discharge. Has the FDA done any sample size  3 calculations of the kind of study that would  4 need to be done to assess cardiovascular risk  5 with a short-term administration?</p> <p>6 I mean, it's conceivable that even  7 a short-term administration could, since we  8 don't know the mechanism, could have a  9 long-term effect if you follow these people.  10 And I just wondered if anyone could give us a  11 sense of what type of a study would be  12 required, and if you've looked at that.</p> <p>13 DR. DANNIS: I think that's a very  14 interesting idea, but at this point, we haven't  15 yet come up with the answer to that question.</p> <p>16 DR. BUCHMAN: Dr. Hennessy? Oh, I'm  17 sorry, Dr. Richardson.</p> <p>18 DR. RICHARDSON: I have a question  19 that I think follows a little bit on what  20 Dr. Kramer had asked, and that is I think  21 relating to the FDA's impression of  22 cardiovascular risk and whether this changed</p>	197	<p>1 risk surfaced? I mean, that would have demanded  2 a little bit more in the way of follow-up.</p> <p>3 DR. KORVICK: I believe for Study 14,  4 we had discussions with the sponsor where we  5 discussed the follow-up and the safety issues  6 for the continuation of that study since it  7 wasn't clear if we would see more events in the  8 long term, and they were close to completing  9 that study. So there were, I believe,  10 re-consents, and there were also attempts to  11 better define for the patients still in that  12 Study 014 more close follow-up. But I think the  13 sponsor can tell you more closely the timetable,  14 but a lot of those patients had completed a  15 significant proportion of the study. So I think  16 that there were mechanisms put in place and we  17 had these kind of discussions.</p> <p>18 DR. BUCHMAN: Dr. Lincoff?</p> <p>19 DR. LINCOFF: I have a question for  20 Dr. Dannis regarding the safety analysis of  21 cardiovascular events. The Kaplan-Meier curves,  22 et cetera, that you presented look a bit</p>

198	<p>1 concerning, but they're based upon the</p> <p>2 non-adjudicated data. In cardiovascular trials,</p> <p>3 we usually use adjudicated data, recognizing the</p> <p>4 difficulties in investigators and the</p> <p>5 variability in sites assessing -- particularly</p> <p>6 myocardial infarction or non-mortal endpoints,</p> <p>7 which have a great degree of objectivity.</p> <p>8       So there's clearly precedent with</p> <p>9 the regulatory agencies for accepting</p> <p>10 adjudicated data's endpoints.</p> <p>11       Now, I recognize that this is a</p> <p>12 post hoc adjudication, but then again, the</p> <p>13 cardiovascular endpoints were all post hoc</p> <p>14 anyhow. They weren't primary endpoints. So</p> <p>15 I'm curious why you chose to do all of your</p> <p>16 analyses with the non-adjudicated data, and</p> <p>17 if you feel that there's a problem with the</p> <p>18 adjudicated data. Because at least from the</p> <p>19 sponsor's presentation, the adjudicated data</p> <p>20 looks much more reassuring.</p> <p>21       DR. KORVICK: We used the</p> <p>22 non-adjudicated data, but I think that the</p>	200	<p>1 non-adjudicated. And that reduces the</p> <p>2 difference quite substantially for the</p> <p>3 non-adjudicated.</p> <p>4       If you look at ischemic</p> <p>5 cardiovascular events, it's 13 versus 6 as</p> <p>6 compared to 14 versus 3.</p> <p>7       That, again, because of the</p> <p>8 differences in the treatment groups,</p> <p>9 virtually eliminates the difference in the</p> <p>10 point estimates.</p> <p>11       So now, other cardiovascular events</p> <p>12 were more similar, but -- so, again, it turns</p> <p>13 out to be -- actually it's 14 adjudicated as</p> <p>14 compared to 8 non-adjudicated, 3 in the</p> <p>15 placebo compared to 2 non-adjudicated for the</p> <p>16 other events, non-ischemic. So at least for</p> <p>17 ischemic events and for total events, the</p> <p>18 adjudication does change the point estimates</p> <p>19 and the relative risks substantially.</p> <p>20       So again, I think that the</p> <p>21 adjudication process should be valid.</p> <p>22 Certainly the people participating in it and</p>
199	<p>1 differences were small. And I'm not sure that</p> <p>2 there were that many differences in the</p> <p>3 different ways that you did the analysis, and</p> <p>4 that's the data we had at-hand at the time.</p> <p>5       DR. LINCOFF: Perhaps I can address</p> <p>6 that because this I think is a key point and I'm</p> <p>7 not trying to perseverate on something</p> <p>8 relatively small.</p> <p>9       But if you look at your Slide, I</p> <p>10 guess, 15 -- it's really 14 and 15, and</p> <p>11 compare it to Table 35 that's presented on</p> <p>12 page 98 of the sponsor's packet -- or</p> <p>13 sponsor's form. So if you look at the actual</p> <p>14 number of events, any cardiovascular -- now,</p> <p>15 the denominator's slightly different, but I</p> <p>16 think relatively small differences and I'm</p> <p>17 not completely clear. I mean, it's 1,800 as</p> <p>18 compared to -- 1,807 in the active treatment</p> <p>19 group compared to 1,728. But if you look at</p> <p>20 the total number of any cardiovascular events</p> <p>21 adjudicated, it's 13 versus -- I'm sorry, 26</p> <p>22 versus 9, and that's 26 versus 4 for the</p>	201	<p>1 the methodology that they reported sound to</p> <p>2 be valid and appropriate, similar to what we</p> <p>3 would use in a cardiovascular trial. And so</p> <p>4 I'm concerned that the non-adjudicated data</p> <p>5 may give us a somewhat skewed result,</p> <p>6 estimate of the cardiovascular risk.</p> <p>7       I'm also interested, on a related</p> <p>8 note, there's been concern about whether or</p> <p>9 not longer-term follow-up of the short-term</p> <p>10 POI studies would have shown a later</p> <p>11 cardiovascular event. I'm unaware of any</p> <p>12 precedent for a short-term drug that led to</p> <p>13 long-term cardiovascular risk. I'm certainly</p> <p>14 happy to -- be pleased to know of a</p> <p>15 precedence that exists, but I don't know of</p> <p>16 any where a five- to seven-day drug then</p> <p>17 leads to an incremental risk of events out</p> <p>18 beyond an immediate post-drug observation</p> <p>19 period.</p> <p>20       DR. DANNIS: I just want to make sure</p> <p>21 that you're comparing -- this table is actually</p> <p>22 patients experiencing the events. So there's</p>

202	<p>1 another table, I think the next slide, which is 2 events. I'm not sure if those numbers are more 3 similar.</p> <p>4 DR. LINCOFF: So that's what I was 5 comparing to Table 35. They have all -- any 6 event, which seems to be what you have on your 7 previous, but perhaps if we just look at -- so 8 that's patients. But if -- so then, if you look 9 at your next slide, so ischemic events, 14 10 versus 3. Adjudicated ischemic events were 13 11 versus 6. Now, that makes a big difference. 12 Because 13 versus 6 comes out .7 percent versus 13 .7 percent.</p> <p>14 DR. DANNIS: What we discovered while 15 doing these analyses is the sponsor did their 16 analyses, adjudication did their analyses, and 17 when we looked at what we had, which was 18 somewhat limited because we just had narratives, 19 we had -- we didn't have complete information. 20 We actually at times got different results. 21 However, what we found were that even though the 22 results were somewhat different, they were put</p>	204	<p>1 DR. BUCHMAN: Dr. Proschan? 2 MR. PROSCHAN: Yeah, again, I want to 3 go back to the comparison of 014 with the other 4 studies. And I notice that the FDA made some 5 different comparisons. One was versus the 6 non-cancer OBD trials, and the other one 7 combined cancer and non-cancer. And I'm 8 wondering whether you think that's reasonable to 9 combine the cancer and non-cancer. It seems 10 like those are quite different.</p> <p>11 DR. HE: For combined non-cancer and 12 cancer patients, we combined them according to 13 the duration of treatment. For the long-term 14 therapy, for the long-term safety data, we have 15 very limited information, because they are both 16 cancer and the non-cancer patient treated, 17 duration is longer. Therefore, we want to do 18 different analyses to see if that more days are 19 still so the signal or not. That is one way we 20 do our safety analysis, so that is why we pooled 21 them together. But we also do the separate 22 analysis, and that is why we put them in here</p>
203	<p>1 in different categories and moved around a 2 little bit, the end result was really the same. 3 And I think it's really difficult when you don't 4 have complete information to have a really great 5 investigation of what went on, but we did do the 6 analysis. And because the end result really 7 wasn't that different, we didn't want to kind of 8 fight over who had angina and who had this 9 because it just seemed like the end result was 10 the same.</p> <p>11 DR. BUCHMAN: Dr. Pasricha? 12 DR. PASRICHA: I want to follow up on 13 the cancer signal. Since the majority of 14 patients in the POI study were being operated on 15 for colon cancer or GI cancer, and given the 16 concern about cancer, if there's any data on 17 survival of these patients -- they're presumably 18 all in a registry of some sort and we should be 19 able to get long-term at least cancer-related 20 outcome data on these patients, and if the 21 agency is thinking of trying to obtain that 22 information, it'd be helpful.</p>	205	<p>1 differently.</p> <p>2 DR. BUCHMAN: Dr. Chang? 3 DR. CHANG: I just wanted to follow up 4 on Dr. Kramer and others' comments about having 5 a short duration of therapy and then maybe 6 having a long-term effect. And I'm just kind of 7 surprised when Dr. Dannis presented the 8 follow-up. In person with the investigator, the 9 patients had so little contact.</p> <p>10 I would think that after a bowel 11 resection, you would come back and see the 12 surgeon in person. So I thought that there 13 must be data out there on a follow-up visit 14 and how they're doing. And if there was 15 any -- if you ask the sponsor to go back, 16 even though it's not standardized and it's 17 retrospective, to go back and look at some of 18 the data.</p> <p>19 And then also, I was thinking that 20 in the opioid bowel dysfunction, most of the 21 trials are short-term, and they may have had 22 follow-up later on in a month or two that you</p>

<p style="text-align: right;">206</p> <p>1 could collect that data, or patients who  2 would rollover in the extension study who had  3 drug. And then, I don't know if there's any  4 of these people that had drug on a short-term  5 study, rolled over in the extension study and  6 had placebo. There's probably not that many  7 of them, but I mean, that's a way to follow  8 them, also. But there's probably ways to  9 collect some of that information out there.  10 DR. DANNIS: Yes. That was one of the  11 questions that I actually had for the sponsor in  12 one of our meetings. I think that what I was  13 presenting was the official protocol-defined  14 visit, where the official information was  15 collected. I'm sure that most of -- if not all  16 actually, probably every single person who had a  17 bowel resection was followed up, and I'm sure  18 that that information is somewhere.  19 However, I don't know if it was  20 collected in a standardized way and whether  21 we have entire information on all the  22 patients.</p>	<p style="text-align: right;">208</p> <p>1 DR. BUCHMAN: The question was where  2 the opioid receptors are located, what part.  3 MR. CHAKRABORTI: Yeah. Opioid  4 receptors are almost located and distributed all  5 over the body, including the CNS. But for this  6 particular compound, they also did a  7 distribution study in rats, a radiographic  8 study, and this drug was not distributed. And  9 I've gone to the central nervous system because  10 I did not cross the (inaudible) barrier walls,  11 so -- because of its structure. So it was  12 mainly distributed in the gastrointestinal  13 tract, and actually locally acting on probably  14 the GI mu-opioid receptors in the gut, and  15 that's all.  16 DR. BUCHMAN: Was there any data on  17 systemic absorption and concentrations of the  18 drug in the bloodstream?  19 MR. CHAKRABORTI: Yes. In the  20 toxicology studies, there was about  21 6 percent -- about 10 percent absorption  22 following oral administration of this drug.</p>
<p style="text-align: right;">207</p> <p>1 DR. BUCHMAN: Dr. Talamini?  2 DR. CHANG: You could probably get  3 that, though, couldn't you? I mean, that might  4 be something good to look at.  5 DR. DANNIS: Yes.  6 DR. BUCHMAN: Dr. Talamini? Last  7 question, Dr. Kramer. Did you have a question?  8 Dr. Epstein?  9 DR. EPSTEIN: Yes, I have a question  10 for Dr. Chakraborti. The mu-opioid receptor,  11 can you describe where that is in the body? Is  12 it in the smooth muscle? Because you mentioned  13 the Purkinje fiber study that the sponsor did,  14 but was there any evidence of any effect on  15 arteries? I know we use morphine, too, in  16 patients with congestive heart failure, et  17 cetera, so I wondered about that.  18 MR. CHAKRABORTI: Mu-receptors are  19 distributed in several organs and tissues. But  20 the -- I'm sorry, I did not follow your question  21 there.  22 Can you tell me one more time?</p>	<p style="text-align: right;">209</p> <p>1 DR. BUCHMAN: And do you have any  2 concern with that in terms of opiate receptors  3 elsewhere outside of the CNS?  4 MR. CHAKRABORTI: They have done in  5 pharmacology studies -- the CNS effects, first  6 of all, in 70 (?) pharmacological studies there  7 is no CNS effects of alvimopan in rats at tested  8 doses, up to 2 milligrams per kilograms.  9 Besides that, they have actually demonstrated in  10 a pharmacological study in mice where the mice  11 were actually treated with morphine and it  12 causes the morphine-induced (inaudible) -- I'm  13 sorry, the (inaudible) morphine-induced infusion  14 of the (inaudible) transit. But it did not  15 cause any effect on the (inaudible)  16 acid-induced. Our writing reflects that is  17 actually morphine was exhibited in that, but it  18 did not actually cause any effect to that. So  19 the (inaudible) for that particular central  20 effect was about 8.7 milligrams per kilogram  21 compared to the morphine's (inaudible) effect  22 was about 0.7. And that gives us a</p>

<p style="text-align: right;">210</p> <p>1 peripheral-to-central ratio of about 127. So  2 that demonstrated pretty much that it actually  3 acts through a peripheral mechanism, so the  4 central action is not our concern.  5 MR. DESEGTER: To answer your  6 question, we don't have any concern about  7 other peripheral opiate receptors.  8 DR. BUCHMAN: Could you identify  9 yourself, please?  10 MR. DESEGTER: Yeah, I'm Shoshan  11 Desegter. I'm the pharmacologist here at FDA.  12 And to answer your question, we don't have any  13 concerns about other peripheral opiate receptors  14 because in toxicology studies, there is no  15 target organs identified even at high doses.  16 DR. BUCHMAN: We're going to take a  17 break for lunch here. We'll be back at 1:00  18 p.m. For the committee, downstairs in the lunch  19 room, there is an area that's roped off with  20 tight security just for committee members.  21 (Whereupon, at 12:00 p.m., a  22 luncheon recess was taken.)</p>	<p style="text-align: right;">212</p> <p>1 greatly from the sponsor on the  2 categorization of the individual patients in  3 terms of cardiovascular events. But what I  4 think what we're seeing with the different  5 analyses that have been presented today, some  6 instability in the data and in the risk  7 estimates that we're wrestling with and that  8 we're going to ask you to wrestle along with  9 us. And that's kind of where I'd leave it at  10 this point.  11 DR. BUCHMAN: Thank you very much.  12 What we're going to use this next period for is,  13 there are a lot of questions that committee  14 members had left for the sponsor. So we're  15 going to allow those to be addressed at this  16 point. And the sponsor can also add some  17 additional information as a rebuttal, if you  18 will. And if we have time in the hour, we'll  19 allow for a re-rebuttal.  20 So with that, I'd like to call on  21 Dr. Hennessy, if he recalls his questions  22 from this morning.</p>
<p style="text-align: right;">211</p> <p>1 AFTERNOON SESSION  2 (1:00 p.m.)  3 DR. BUCHMAN: Okay, good afternoon. I  4 hope everybody enjoyed their lunch.  5 The original schedule has for an  6 open public forum as we typically do at these  7 sessions, although no one from the public has  8 registered. So therefore, we're going to  9 dispense with that. That gives us an extra  10 hour of discussion, and I think there are  11 some important points that we need to address  12 that are going to be used before we get to  13 the questions.  14 I'd like to reintroduce Joyce  15 Korvick, who will address some of the  16 concerns that were raised this morning about  17 the cardiovascular risk profile from Entereg.  18 DR. BEITZ: I'll just read sort of a  19 summary of where we are after this past hour of  20 sort of discussion regarding the different  21 analyses that have been presented.  22 So we essentially don't differ very</p>	<p style="text-align: right;">213</p> <p>1 DR. HENNESSEY: Great, thank you. I  2 have two questions. One has to do with the size  3 of the population that's likely to be exposed to  4 the drug if it's approved. So one obvious  5 population is people who have had gut surgery.  6 How large a population is that likely to be per  7 year? And also, it seems likely that the drug  8 would be used for non-gut surgery. For example,  9 orthopedic surgery, where there's lots of opiate  10 use after surgery. And I'm wondering if the  11 drug is used off-label, how large the population  12 of people that is likely to get it off-label.  13 DR. BUCHMAN: Please identify yourself  14 when you speak for the transcriber.  15 DR. JACKSON: This is David Jackson  16 from Adolor. I'm going to ask Dr. Senagore to  17 address the question about numbers of potential  18 surgical patients.  19 DR. SENAGORE: Anthony Senagore,  20 Spectrum Health, Grand Rapids, Michigan. The  21 labeling is requesting for colectomy, and  22 national numbers are somewhere in the range of</p>

<p style="text-align: right;">214</p> <p>1 about 400,000 per year for all diseases. And of  2 that, still in this country, about 90 percent of  3 those are done by open surgical techniques. So,  4 it would be about 350,000 to 360,000 patients.  5 In terms of the off-label, I'll leave that to  6 the sponsor to discuss.  7 DR. BUCHMAN: Thank you. Dr. Epstein?  8 DR. EPSTEIN: Yes, my question to the  9 sponsor is, was there any sub-analysis done of  10 patients with diabetes? One of the biggest  11 clinical problems we face is individuals with  12 diabetes having a significant risk to develop  13 prolonged motility disorders. And I wonder if  14 there was any look at the data regarding  15 diabetes, and how that impacted on the trial and  16 the clinical endpoints.  17 DR. JACKSON: Thank you. Dr. Techner?  18 There are significant numbers of patients in the  19 database who did indeed have diabetes.  20 DR. TECHNER: If I could just have the  21 slide on baseline cardiovascular risk factors  22 and POI population. I think that's an</p>	<p style="text-align: right;">216</p> <p>1 tendency to get postoperative ileus regardless.  2 And I wonder if the clinical effect would be  3 stronger in that population or if you have any  4 data? Do you have any data on that  5 particularly?  6 DR. TECHNER: We do not have data on  7 that. But that's certainly something we could  8 look at in the future.  9 DR. BUCHMAN: Dr. Pasricha?  10 DR. PASRICHA: As sort of a related  11 question to that, can you please clarify whether  12 the outcomes were analyzed with your modified  13 intention to treat equally all patients whose  14 discharge was potentially delayed for non-GI  15 problems as well, or only included GI-related?  16 DR. TECHNER: No, our analyses  17 included all patients, regardless of whether  18 they were readmitted or their hospital stay was  19 prolonged for a GI or non-GI event.  20 DR. PASRICHA: So was that a  21 significant proportion of patients whose  22 discharge was delayed because of non-GI</p>
<p style="text-align: right;">215</p> <p>1 interesting question. And one of the things we  2 have looked at is the proportion of patients who  3 in fact did have diabetes. And I think what you  4 can see here is that somewhere between 10 and  5 14 percent, whether it be the overall population  6 we're looking at or the bowel resection  7 population only, had recorded baseline  8 comorbidity of diabetes.  9 So proportionally, it was about the  10 same across treatment groups. We did not  11 look at the treatment effect specifically in  12 that subgroup. However, one would suspect  13 that if that was a factor in any way,  14 shape, or form, it would be affecting both  15 the placebo and the alvimopan treatment  16 groups similarly. The other thing is, I  17 believe what you're referring to is not  18 really a narcotic-induced condition. And  19 again, alvimopan is a highly selective  20 mu-opioid receptor antagonist.  21 DR. EPSTEIN: Yes. And I guess  22 nevertheless, those patients do have a higher</p>	<p style="text-align: right;">217</p> <p>1 complications?  2 DR. TECHNER: I believe that I would  3 really have to say that the majority of  4 patients, the primary reason for a delay  5 discharge was unresolved ileus, which is, as  6 you've heard from Dr. Senagore, consistent with  7 what surgeons see in practice.  8 DR. PASRICHA: I guess what I'm trying  9 to see is if the effect was even larger if you  10 carved out the non-GI complications.  11 DR. TECHNER: We did not look at the  12 data that way. But again, this is certainly  13 something we could look at in the future.  14 DR. BUCHMAN: Dr. Talamini, you had a  15 question regarding the use of ketorolac and  16 other -- perhaps a group of patients that did  17 not receive narcotics?  18 DR. TALAMINI: Yes, so my question  19 was, particularly in the European study, where  20 that drug was indeed used, whether you had  21 enough data to analyze that group separately,  22 and if so, what the effects were. Again,</p>

218	<p>1 because in context, I think in this country,  2 many surgeons use that as a strategy to reduce  3 overall opioid postoperative use and get the  4 patients out of the hospital a little bit more  5 quickly. So it's a similar strategy.  6 DR. TECHNER: How about -- I think the  7 way we'll answer your question is twofold. I'll  8 address it from a data perspective, and then I'd  9 like to have Dr. Senagore address it from what  10 is commonly used in practice today. You are  11 correct, in the European study -- in the  12 non-U.S. study, I should say, the range of  13 opioid use and opioid-sparing technique was  14 broad. It varied from country to country. So  15 we would have countries, for example, where we  16 saw virtually no opioids being used. And in  17 those situations, as you would expect, the  18 effect of Entereg was minimal to countries where  19 the use of opioids was comparable to what we see  20 in the States.  21 So I think -- and this goes back to  22 an earlier question -- is there a threshold,</p>	220	<p>1 that Dr. Senagore can address that as well. And  2 I think this goes back to what is the etiology?  3 What are the mechanisms involved in ileus? So  4 Tony, if you would address that, please.  5 DR. SENAGORE: Yeah, I think probably  6 the 001 study gives us guidance on that, because  7 there are truly no regimes that are devoid of  8 narcotic administration in patients undergoing  9 major laparotomy. But as I discussed, the  10 etiology of ileus is multifactorial. So it may  11 be that the group that gets an NSAID is actually  12 abrogating the effects of the inflammatory  13 component that leads to ileus, and now you're  14 seeing an added benefit from blocking the  15 narcotic component. So even in Europe, patients  16 still do get modest doses of narcotics, of which  17 you did see benefit in the 001.  18 DR. BUCHMAN: Dr. Kramer?  19 Dr. KRAMER: Judith Kramer from Duke.  20 Actually, my question is for Dr. Senagore as  21 well, but it's very similar. It's really a  22 follow-up on what Sean raised. And my question</p>
219	<p>1 if there is virtually no opioid on board,  2 then we would not expect this drug to have  3 much benefit.  4 I'd like to ask Dr. Senagore to  5 come up just to address common practice with  6 respect to pain management in these patients.  7 DR. BUCHMAN: You know what? Before  8 Dr. Senagore addresses us, I just want to follow  9 up on your comment with regard to a question I  10 had earlier --  11 DR. TECHNER: Sure.  12 DR. BUCHMAN: And something that we'll  13 perhaps discuss a little bit later. But what is  14 the sponsor's feeling in terms of the labeling?  15 Is this really a postoperative ileus that you're  16 treating? Or in view of your most recent  17 comment, perhaps that's incorrect. Perhaps it's  18 a narcotic-induced, specifically a  19 narcotic-induced postop ileus that you're  20 treating. And is that more appropriately the  21 indication that you seek?  22 DR. TECHNER: You know what? I think</p>	221	<p>1 is, as a surgeon who is very familiar with this  2 drug, would you expect that if this were  3 marketed, that surgeons would prescribe it to  4 prevent and treat postoperative ileus plus other  5 types of abdominal surgery besides bowel  6 resection?  7 DR. SENAGORE: Well, if you look at  8 the data, at least for laparotomy, what  9 operations lead to the highest rate of  10 postoperative ileus, it really is bowel  11 resections, both large and small. And so for  12 our general surgical community, that would be  13 the most common indication. Could this drug be  14 advantageous in other operations that use high  15 doses of narcotics, like spinal surgery or total  16 joint reconstruction? It's plausible, but I  17 don't know that we have data at this point to  18 say that.  19 DR. BUCHMAN: Would you foresee the  20 use of this medication in a postoperative ileus  21 in a patient that had a abdominal aortic  22 aneurism repair or had other baseline</p>

<p style="text-align: right;">222</p> <p>1 cardiovascular risk issues?  2 DR. SENAGORE: Again, I don't think  3 that there's data to say convincingly that it  4 would work there, but certainly if you pull the  5 expectation that, again, these patients have a  6 major incision, high doses of narcotics, it's  7 plausible to believe there would be a benefit in  8 that population as well.  9 DR. BUCHMAN: Dr. Lincoff?  10 DR. LINCOFF: I'd just like to  11 continue the same line of questioning I was  12 discussing with the adjudicated endpoints. I  13 wonder if you have any more data that you can  14 show us specifically for Study 14 with the  15 adjudicated endpoints? I mean, given really  16 that Study 14 is the reason that we're having I  17 think all of this discussion on the  18 cardiovascular endpoints, and that there is a  19 small number of events that differ between the  20 adjudicated and the non-adjudicated that  21 nevertheless changed the odds ratios fairly  22 substantially. And the point estimates, which</p>	<p style="text-align: right;">224</p> <p>1 chronic constipation study, so it's strictly the  2 OBD population. It changes the denominators  3 slightly, and I think you recognized that when  4 comparing the graphs.  5 So here are the results expressed  6 in terms of events and patients, and this  7 relates to ischemic events. And I should  8 point out at this point that the ischemic  9 composite that was assigned prior to doing  10 this analysis was somewhat different to the  11 FDA ischemic composite, because it contained,  12 in addition to myocardial infarction,  13 unstable and new angina, and stroke, it also  14 contained ischemic heart failure and TIA and  15 sudden cardiac death and cardiac arrest,  16 which was deemed to be ischemic in origin.  17 So you can see here that any  18 ischemic event, in terms of events, was 8  19 versus 14 for the whole program. And the  20 number of patients was 6 versus 13. That is  21 roughly equivalent. But you can see that  22 there is a numerical imbalance in terms of</p>
<p style="text-align: right;">223</p> <p>1 is, of course, a good indicator of the  2 instability of these estimates in the first  3 place with small numbers. But how much of the  4 data that was in the table, that is in your  5 book, and that you had shown, how much of that?  6 Could we see that for 14, which is really where  7 most of the analyses that the FDA has done with  8 the unadjudicated data focused on? What can you  9 show us in terms of breakdown, the components of  10 the ischemic endpoints, et cetera?  11 DR. JACKSON: Let's try and get to it.  12 Dr. Camm?  13 DR. CAMM: Thank you very much,  14 Dr. Lincoff. First of all, I'd like to see the  15 data for the adjudicated events, the ischemic  16 events, for the entire OBD database, and I think  17 that's in OC 44. This is the data of the  18 adjudicated events for the whole OBD program.  19 Now, I mean by that not exactly the same  20 population as Dr. Dannis analyzed, because it  21 didn't include the clinical pharmacology  22 studies, and it didn't include the idiopathic</p>	<p style="text-align: right;">225</p> <p>1 acute MI, which was contributed to very  2 largely by the GSK014 study, and that in  3 percentage terms was 0.24 with placebo and  4 0.44 with patients.  5 New onset unstable angina also  6 showed potentially an imbalance, at  7 0.12 percent versus 0.22 percent. But as you  8 can see, the numbers are very small, and any  9 oscillation in terms of the assignment would  10 make a big difference to the ratios in either  11 the acute MI or in terms of the new onset or  12 unstable angina.  13 I'm not sure whether you also have  14 a slide for the GSK014. Do you have that  15 available? Here, you can see just in the  16 number of studies, one by one, going from  17 011, 012, 013, and 014, the difference  18 between placebo and alvimopan with respect to  19 ischemic cardiovascular events. And you can  20 see in 014, it was 9 versus 0 ischemic events  21 when adjudicated by the IDMC.  22 And I think I shouldn't go past</p>

<p style="text-align: right;">226</p> <p>1 this point without remarking on the fact that  2 zero events in the placebo group is pretty  3 unusual, given that this group of patients  4 was relatively high risk for cardiovascular  5 events. And the events seen with alvimopan  6 are not necessarily out of context with  7 chronic opioid bowel disorder.  8       So those, I think, answer the  9 question that you put to me.  10       DR. BUCHMAN: Ms. Corkery-DeLuca?  11       MS. CORKERY-DELUCA: Yes, my comment  12 and question would be related to Dr. Lincoff's.  13 Looking at the diabetes population, I think one  14 of the more popular upcoming surgeries is  15 bariatric, a bowel resection to alleviate  16 diabetes. So who handles that?  17       Who's in charge?  18       DR. JACKSON: Well, I'm going to have  19 a surgeon answer the question for you.  20       DR. SENAGORE: I don't do that surgery  21 anymore, but that population actually has a  22 very, very low rate of postoperative ileus. In</p>	<p style="text-align: right;">228</p> <p>1 think that was quite what Dr. Lincoff asked for,  2 at least it's not what I was thinking. Because  3 what you didn't show was the MI, patients with  4 MI, in the 014 adjudicated. And I'm wondering  5 if you have that slide and that information?  6       DR. BUCHMAN: Do you have that, Eric?  7       DR. MORTENSEN: Eric Mortensen, GSK.  8 I'll see if we have a slide to bring up. But  9 essentially, I can say to you is that all seven  10 of the myocardial infarctions that occurred in  11 014 were positively adjudicated. I mean, I  12 wouldn't bother showing the slide. Essentially,  13 and as I noted before, they all occurred in  14 patients who were then confirmed to have had  15 pre-existing cardiovascular disease.  16       DR. BUCHMAN: Dr. Cullen?  17       DR. CULLEN: Joe Cullen from  18 University of Iowa. One question on the  19 postoperative ileus studies: Were the use of  20 prokinetics, like Reglan on a scheduled basis,  21 or antiemetics or suppositories allowed in the  22 study protocols? And if so, was there</p>
<p style="text-align: right;">227</p> <p>1 fact, if you look at the U.S. data, I think  2 probably the mix today is probably 90 percent or  3 greater laparoscopic versus open. And the rate  4 of ileus is very low. The length of stay is  5 under two days in the U.S. for that operation.  6       MS. CORKERY-DELUCA: So it would be a  7 move forward.  8       DR. SENAGORE: Well, again, I'm not  9 sure that this drug would be an advantage in  10 that population, because they're laparoscopic,  11 very small incisions, and they're home so  12 quickly that they're on to other alternative  13 treatments.  14       DR. BUCHMAN: Are you suggesting,  15 then, that the drug be limited to use in  16 patients with open bowel surgeries?  17       DR. SENAGORE: I guess I can leave  18 that to the sponsor to comment on what they're  19 asking for on the labeling.  20       DR. BUCHMAN: Dr. Proschan?  21       DR. PROSCHAN: I just wanted to follow  22 up on the question previously, because I don't</p>	<p style="text-align: right;">229</p> <p>1 equivalence between placebo and drug?  2       DR. TECHNER: In order to address your  3 question, let me answer it in two ways. One, in  4 general, the prophylactic use of antiemetics, et  5 cetera, generally was as per hospital standard.  6 So in general, we did not restrict to any  7 significant extent across the board the use of  8 those medications. However, if we look at the  9 use of those medications, in other words, all  10 medications where we feel their use may have in  11 some way, shape, or form impacted GI function,  12 5HT3s, metoprolamide, erythromycin, laxatives,  13 cathartics, 5HT4, and any other antiemetics, I  14 think you can see here that it was very  15 well-balanced across treatment groups. So if  16 there was some effect, we would basically expect  17 it to be a wash between a placebo and the  18 alvimopan treatment.  19       DR. BUCHMAN: A related question.  20 Electrolyte abnormalities have been demonstrated  21 quite frequently to have a role in the  22 development and prolongation of postoperative</p>

230	<p>1 ileus. I would assume that you have data on  2 potassium, magnesium, and calcium in these  3 patients, and if so, were they similar between  4 groups?  5 DR. TECHNER: We do have that data in  6 our adverse event database, and they were  7 similar across treatment groups.  8 DR. BUCHMAN: Dr. Levine?  9 DR. LEVINE: Just one possible  10 confounding variable with the cardiovascular  11 events. I wonder if you can tell me about the  12 geography of Europe? Was this Western  13 Europe-limited or was it all of Europe?  14 DR. MORTENSEN: I'm not sure. What do  15 you have in mind? What kind of a subissue is  16 it?  17 DR. LEVINE: I'm specifically asking  18 if there are any -- if Eastern Europe  19 investigators were involved in this.  20 DR. MORTENSEN: In Study 001 or in the  21 014 study?  22 DR. LEVINE: In any of the non-U.S.</p>	232	<p>1 DR. MORTENSEN: We'll be happy to get  2 that information. I am sorry I don't have that  3 information for you.  4 DR. LEVINE: Was it a small number?  5 Was it a modest number? Can you give us some  6 idea?  7 DR. MORTENSEN: The total number of  8 patients randomized from Eastern Europe was  9 relatively small. The majority of the patients  10 overall for the entire 14 study, the majority  11 came from the United States. I don't have --  12 DR. LEVINE: No, I'm talking about the  13 non-United States studies.  14 DR. MORTENSEN: No, I understand it.  15 I'm just saying that the total composition for  16 014 -- did you say 001 or 014?  17 DR. LEVINE: Either one, actually.  18 I'd like to know the numerical number  19 approximately of the Eastern European  20 investigators versus the Western European  21 investigators, for possible obvious reasons.  22 DR. MORTENSEN: Okay. I don't have</p>
231	<p>1 Studies.  2 DR. MORTENSEN: Can I have the slide  3 that shows the distribution of sites for 014?  4 What I'll start out just by noting is I didn't  5 mention in my core presentation that of the  6 seven events, that five were Cluster II sites.  7 We don't know what it means, but we have known  8 that three of those events did occur at a site  9 in Glasgow, which is a region that is  10 particularly marked to have a very high rate of  11 cardiovascular disease incidence.  12 We did have sites also -- I'm still  13 not seeing the slide coming up -- we did have  14 sites extended across Eastern Europe, but we  15 did not have anything in the Soviet Union.  16 Are you done with the slide? Number 14. We  17 did include sites in both Eastern and Western  18 Europe, but we did not include the former  19 Soviet Union countries.  20 DR. LEVINE: I'd like to know the  21 number of the total subjects that were in  22 Eastern Europe versus Western Europe.</p>	233	<p>1 that answer for you immediately for 014. I will  2 be happy to get that information by the time of  3 the second review. I'm not sure, Lee, if you  4 have a slide that speaks to the issue in 001.  5 DR. TECHNER: Let's see if this  6 potentially answers your question. How about  7 let's look at the slide of opioid use by  8 country. Yeah, that should do it.  9 So on Study 001, here is a list of  10 countries involved. What you see here is the  11 proportion of patients that came from that  12 country, and this is really the use of PCA  13 opioids within the first 48 hours by country.  14 So the purpose of the slide is a bit  15 different, but at least it gives you a  16 breakdown of where the patients were divided  17 across countries. You see certainly, if you  18 were in Greece, that might be a bit of an  19 issue.  20 DR. BUCHMAN: Dr. Kramer, did you have  21 a follow-up question on that?  22 DR. KRAMER: Yes, I just had a</p>

234	<p>1 follow-up question. The sponsor is pointing out  2 that three of the patients were at a single site  3 in Glasgow, and there was a high incidence of  4 cardiovascular disease. But is there any reason  5 to think that there weren't also placebo  6 patients of equal balance in that site? Was  7 that site somehow randomized such that they were  8 all alvimopan?</p> <p>9 DR. MORTENSEN: No, we actually --</p> <p>10 DR. BUCHMAN: Please state your name  11 for the record.</p> <p>12 DR. MORTENSEN: Eric Mortensen,  13 GlaxoSmithKline. No, we did look to see whether  14 or not the two sites that represented the  15 majority of the myocardial infarctions showed  16 perhaps any alteration imbalance. There was no  17 evidence of an imbalance with regard to  18 randomization. We simply mention this to note  19 that it is a somewhat unusual clustering and we  20 cannot rule out potentially differences in  21 regional practice in terms of the number of  22 patients with high risk that may have been</p>	236	<p>1 receptors, had some kind of tumor-inhibiting  2 effect, like it's believed that endorphins  3 may help cancer patients. But is there any  4 studies, either by the FDA or sponsor, that  5 people know of where the mu-opioid receptor  6 plays a role in tumor inhibition or growth,  7 and might that blocking that receptor may  8 play a role in enhancing tumor growth?</p> <p>9 DR. TECHNER: Lee Techner, Adolor.  10 Let me address the first part of your question,  11 the efficacy part. And I'm going to do it, if  12 you don't mind, in two ways. I'll present our  13 thoughts, a bit about our thoughts, and then I'd  14 like to have either actually Dr. Senagore or  15 Dr. Delaney come up and give you their clinical  16 perspective. May I have my slide showing GI-2  17 recovery, the Kaplan-Meier curves, please?</p> <p>18 I think one of the important things  19 to consider here is that when we set out to  20 design these trials and evaluate these  21 patients, we really wanted to look at the  22 10-day period where we knew things were</p>
235	<p>1 randomized at the trial.</p> <p>2 DR. BUCHMAN: Dr. Chang?</p> <p>3 DR. CHANG: Hi. I have an efficacy  4 question and a safety question. The efficacy  5 question is about whether the treatment effect  6 is clinically meaningful. And I would think  7 that the unmet need is more of these patients  8 with prolonged postoperative ileus, and I  9 suppose that's your 75th percentile where you  10 show a one day earlier discharge. To me, that  11 seems clinically meaningful.</p> <p>12 I don't think a half-day seems  13 clinically meaningful, but I was wondering  14 how the sponsor determined that. Is that  15 based on a survey with surgeons or with  16 patients or a cost-effective analysis? How  17 is that determined? That's the first one.</p> <p>18 The safety issue is really based on  19 this issue about neoplasm. And I was  20 wondering if, like in colitis, immune cells  21 release opioids, and I don't know for tumors  22 if the opioid receptors, the mu-opioid</p>	237	<p>1 happening. They were recovering from their  2 ileus, if you will. And so we followed them  3 along this period. And I think what you can  4 see here is that clearly, regardless of  5 whether patients are down in this part of the  6 curve or up in this part of the curve, which  7 really corresponds to about Day 5 or 6,  8 which, as I think you've heard from  9 Dr. Senagore, is the period of time where  10 that red flag starts to go up in their heads,  11 that the alvimopan curve is always to the  12 left of the placebo curve.</p> <p>13 And so yes, we do see what appears  14 to be the most robust difference at around  15 the 75th percentile, Day 5 and 6, which I  16 think is very clinically appropriate. But we  17 also see that patients all along this curve  18 are doing better.</p> <p>19 And so I think certainly from our  20 perspective, we feel that if we can get  21 patients to achieve GI recovery earlier so  22 that they can eat earlier, so that their</p>

<p style="text-align: right;">238</p> <p>1 nutritional status improves, they're up and  2 around earlier, that to us likely is very  3 important to the patient and likely important  4 to these guys.  5       So how about if we bring  6 Dr. Delaney up here and allow him to address  7 this from his perspective?  8       DR. DELANEY: Conor Delaney, Case  9 Western Reserve University. Actually, one day  10 is probably quite a clinically meaningful  11 endpoint. That's something that's really  12 evolved over the last decade in this type of  13 research. First, from the patient's point of  14 view, obviously every day less in hospital is a  15 nice thing for them. And from the institution's  16 point of view, it's useful as well. You have  17 not only that bed available, but you have the  18 opportunity to bring someone else into that  19 hospital bed. The one day is useful, and it's  20 become valid enough that it's now really the  21 endpoint that's been used for many of the other  22 studies that we do on postoperative ileus,</p>	<p style="text-align: right;">240</p> <p>1 presented, it approximates one day. What I  2 think you have to remember when you look at the  3 Kaplan-Meier curves is that it's not a shift to  4 the left for one day for every patient, but it's  5 particularly the patients who have the longer  6 complicated postoperative ileus that were  7 improving.  8       So yes, maybe for a certain  9 percentage of the patients, they only go home  10 or are ready to have a discharge order  11 written two hours earlier, and no, that's not  12 going to matter much for the hospital. But  13 for the patients who really make the  14 difference to shifting that mean, or the  15 patients who stay seven days instead of nine,  16 and that's opportunity for the hospital, but  17 particularly important for the patient. And  18 then the other spin on it is that they end up  19 being less likely to be readmitted with ileus  20 symptoms. So I think the effect is seen in  21 multiple places.  22       DR. BUCHMAN: If we contrast that 75th</p>
<p style="text-align: right;">239</p> <p>1 looking at different types of postoperative care  2 pathway. So one day has become reproducibly an  3 effective endpoint for that reason.  4       DR. BUCHMAN: One day is 24 hours.  5 Hospitals don't function like cheap hotels where  6 you pay by the hour. So is one day 24 hours; is  7 that the same as 22 hours? Is that the same as  8 25 hours?  9       Or in the current billing  10 structure, if we're going to save money and  11 get people out earlier, it seems to me that  12 we're really stuck at 24 hours here. Because  13 otherwise, if they're there for 24 hours and  14 30 minutes, they've paid for that second day.  15       DR. DELANEY: Right. And I think  16 that's a very important point to raise, whether  17 it's 12 or 18 or 20 or 22 or 24. I think what  18 we see with all the multiple types of data  19 analysis that have been presented is that  20 whatever way you look, whether it's recovery of  21 GI-2 or GI-3 or discharge order written or  22 average mean length of stay, which you also saw</p>	<p style="text-align: right;">241</p> <p>1 percentile to the mean and median data, if  2 indeed there's this full-day benefit for the  3 75th percentile, which is quite different from  4 that which we see with a mean or median patient,  5 to me that suggests that there are patients on  6 the other end who actually stay longer with the  7 Entereg medication.  8       Have you evaluated -- what's the  9 25th percentile group, for example? Is there  10 a longer stay in some of those patients?  11 Because how do we see such a difference  12 between the 75th percentile and the mean?  13 And also, how do you explain the difference  14 between the mean and median? The median, of  15 course, would alleviate the outlier data.  16       DR. TECHNER: Let me see if I can  17 address that question for you. Can I please see  18 the core slide that I showed the committee on  19 the Kaplan-Meier curves for discharge order  20 written, please? Very much like the GI recovery  21 curves that I showed you, the same pattern  22 applies to the discharge order written curves.</p>

<p style="text-align: right;">242</p> <p>1 And so I think what you're seeing here -- and  2 remember, as I discussed before, we see this  3 cyclical pattern in these curves just as a  4 result of the pattern of when discharge orders  5 were written clinically.  6 But I think you see the same thing.  7 And that is that all time points, from about  8 between Day 2 and Day 3, which is when some  9 patients do get out -- now, we don't know if  10 these folks are coming back with unresolved  11 ileus. Maybe they were discharged too early;  12 we don't know that. But from here all the  13 way through the entire 10-day observation  14 period, the alvimopan curve stays to the left  15 of the placebo curve. So there is no point  16 along here where we see patients receiving  17 Entereg doing worse than placebo. So I think  18 that addresses one point.  19 I think the other point that I'd  20 like to make is, you mentioned the difference  21 between the median, et cetera. Can we just  22 please leave that up? Thank you. Okay. I</p>	<p style="text-align: right;">244</p> <p>1 is that we don't know who's going to be here  2 and who's going to be here. And I think  3 that's the biggest dilemma that these guys  4 face, not only from a GI recovery  5 perspective, but also from a discharge  6 perspective.  7 I think if you asked Drs. Delaney  8 or Senagore to predict which one of their  9 patients is going to have earlier GI recovery  10 or later GI recovery or earlier discharge or  11 later discharge, they will tell you they  12 cannot do that. So I think that's also an  13 important item to remember.  14 DR. BUCHMAN: Dr. Talamini?  15 DR. TALAMINI: I'm not exactly sure  16 how to ask this, but the construct that we're  17 dealing with today is built upon the belief that  18 once a patient is having bowel movements after  19 an anastomotic procedure, that they're okay and  20 they can go home. And all the surgeons in the  21 room have been trained to believe that because  22 we believe that once the bowel's functioning,</p>
<p style="text-align: right;">243</p> <p>1 see what you're trying to do. You know,  2 again, I think when you look at the median  3 versus when you look at the means, you're  4 looking at two different measures. The  5 median, you're looking at one time point  6 across this entire early perioperative  7 recovery period.  8 And it may be that at that  9 particular point in time, the curves are  10 either very close together or they're either  11 very far together, and that's going to have  12 an impact on your median. And that's why,  13 from our perspective, we believe that the  14 mean, the Kaplan-Meier mean, meaning the  15 difference between these two treatment groups  16 over the entire 10-day observation period, is  17 more appropriate for looking at what Entereg  18 is really doing with respect to either GI  19 recovery or discharge order in this  20 particular population.  21 And the third thing I'd like to  22 add, in follow-up to Dr. Delaney's statement,</p>	<p style="text-align: right;">245</p> <p>1 the anastomosis is okay. That probably isn't  2 really true.  3 And the reason I bring it up is  4 that that right now is what keeps patients in  5 the hospital, and if that turns out not to be  6 true, there will be a push to send bowel  7 anastomosis patients home when they're on  8 liquids, much like your hysterectomy patients  9 went home when they were on liquids, which  10 would change this whole idea of this drug  11 only being given when patients are in the  12 hospital.  13 I wonder if you've thought about  14 that or anticipated it, because there are  15 some early studies of bowel surgery patients  16 going home before they have their first bowel  17 movement.  18 DR. TECHNER: I think that's an  19 important question. And I think I'd like to ask  20 Dr. Delaney to respond to that from his clinical  21 perspective. I can tell you that certainly, in  22 our studies, in polling all of these surgeons as</p>

<p style="text-align: right;">246</p> <p>1 to what criteria they use to discharge their  2 patients -- now understand, this spans a period  3 of time between 2001 and 2006 -- consistently,  4 consistently, their definition of GI recovery  5 usually includes both tolerating solids and the  6 occurrence of a bowel movement.  7 So I'll let Dr. Delaney address  8 that for you.  9 DR. DELANEY: Conor Delaney, Case  10 Western. I think Dr. Techner has really partly  11 addressed your answer. But I think we also have  12 to remember that the GI-2 or GI-3 endpoint  13 includes tolerance of diet. And while yes,  14 there are protocols to discharge patients early  15 from hospital while they're just on liquids,  16 first, it certainly would be routinely accepted  17 and it would be quite an aggressive discharge  18 policy to follow.  19 And second, that that depends on  20 the patient's being able to adequately  21 tolerate oral intake sufficient to be able to  22 maintain hydration at home. So this would</p>	<p style="text-align: right;">248</p> <p>1 Is that correct?  2 DR. TECHNER: That is correct. And  3 the reason, because they contain either all, or  4 mostly all, bowel resection patients.  5 DR. KRAMER: Bowel resection, right.  6 The next slide, the one that has the actual  7 individual studies.  8 DR. TECHNER: The actual mean, median,  9 et cetera.  10 DR. KRAMER: That's CA 38.  11 DR. TECHNER: Yes. Go ahead and put  12 that up.  13 DR. KRAMER: I'm concerned about the  14 representation of how you counted the median  15 there. If we just look at Studies 313 and 314,  16 the median difference from placebo is 7.8 and 6  17 hours; is that correct?  18 DR. TECHNER: That is correct.  19 DR. KRAMER: And the mean is clearly  20 affected by outliers, and the 75th percentile by  21 definition are the outliers. So I just feel  22 like when we consider the risk and benefit, we</p>
<p style="text-align: right;">247</p> <p>1 suggest that this is still going to help from  2 that point of view. It's not just passing a  3 bowel movement, but also being able to  4 tolerate diet earlier, that this medication  5 can help that.  6 And then finally, the concern with  7 being too aggressive about discharging people  8 is that they may be more likely to be  9 readmitted. And so that's perhaps I think  10 why many people do wait for GI function to  11 occur before they discharge patients. And  12 again, this is somewhere this may be able to  13 help us in practice.  14 DR. BUCHMAN: Dr. Kramer?  15 DR. KRAMER: Judith Kramer from Duke  16 University. I'd like to follow up on  17 Dr. Buchman's question again concerning if you  18 could go back to that slide, CA 38, where you're  19 trying to show the medians in the different  20 studies. If I understood your presentation  21 correctly in the packet, 314 and 313 are major  22 efficacy studies in your application.</p>	<p style="text-align: right;">249</p> <p>1 really need to consider how many patients we're  2 asking to take this drug with an unknown  3 cardiovascular risk, I would say at this point,  4 in order to obtain the benefit in the patients  5 at one end of the spectrum. So I don't think we  6 should discount the median benefit. So if you  7 line up all the numbers, it's right in the  8 middle, and the most common kind of response is  9 going to be on order of magnitude less in terms  10 of the clinical meaning of it.  11 DR. TECHNER: Let me address your  12 question two ways, if you would. I'll give you  13 just a brief perspective for myself. And then  14 I'd actually like Dr. Koch to come up and give  15 you a perspective of the mean, the median, et  16 cetera, from a practical standpoint. I think  17 that we certainly are not discounting the  18 median. And in no way, shape, or form, and if  19 it came across that way, I will certainly  20 apologize, that the median is not valid  21 statistically. I think what we're trying to say  22 is in order to evaluate the effect, the</p>

250	<p>1 treatment effect of alvimopan in this  2 population, we believe that the mean is one  3 important measure that we focus primarily on,  4 and that the median, and at the 75th percentile,  5 provide additional information to support the  6 mean based on the differences between the two  7 treatment groups.</p> <p>8 So we're not dismissing the median.  9 We're trying to look -- and as a matter of  10 fact, we're trying to present you with all  11 the data. But I think maybe it would help to  12 have a little more of a perspective from  13 Dr. Koch as far as the practicalities of  14 looking at medians and means to help you  15 understand this maybe a little differently.</p> <p>16 DR. KOCH: Gary Koch, Biostatistics  17 Department, University of North Carolina. Can  18 we go back to CA 31, with the area filled in?  19 So as you can see, Kaplan-Meier curves wiggle.  20 And when you pick a particular quantile like the  21 median, you make pick a quantile where they are  22 randomly somewhat closer together, or you may</p>	252	<p>1 curve or non-event curve. And when you have  2 two groups that you're comparing, the  3 difference in means is the area between the  4 Kaplan-Meier curves. Now, when we work with  5 the difference in means, we're actually  6 looking at the horizontal distance between  7 the curves at every quantile, and then  8 averaging them together as we move up. And  9 we're taking into account what the  10 differences are at every quantile and  11 averaging them together.</p> <p>12 The difference in means is actually  13 an underestimate of what the actual  14 difference is, because the difference in mean  15 estimate is truncated at 264 hours. So it is  16 not leveraged by outliers beyond 264 hours.  17 It actually is a truncated mean calculated  18 through 264 hours. And because alvimopan is  19 still better through 264 hours, the estimates  20 that you're seeing for the difference in  21 means is actually an underestimate of what  22 the means would be if you went the full</p>
251	<p>1 even pick one up down here, where they may be  2 randomly somewhat further apart. So picking a  3 single quantile to emphasize isn't really that  4 much different than picking a particular time  5 point, like 72 hours in comparing proportions,  6 or 96 hours in comparing proportions, or 120  7 hours in comparing proportions.</p> <p>8 The different hours along the time  9 course are arbitrary landmarks, although some  10 may be more meaningful than others. And  11 there has been some mention here that five  12 days was a meaningful landmark along the time  13 course. And some quantiles may be of more  14 interest than others. And we've had  15 discussion of the 25th percentile, the 50th  16 percentile, which is the median, and the 75th  17 percentile.</p> <p>18 Now, we also have been emphasizing  19 more the difference between the means than  20 the means per se. When you have a  21 time-to-event curve, the mean is actually the  22 area under the Kaplan-Meier survivorship</p>	253	<p>1 distance.</p> <p>2 So the main advantage of the mean  3 is that it's basically integrating all of  4 these horizontal distances between the two  5 curves at their respective quantiles  6 together, and producing what can be  7 interpreted as the average amount of benefit  8 that a patient might expect, comparing one of  9 the arms to the other arm.</p> <p>10 DR. BUCHMAN: In terms of -- leaving  11 this up for a minute, the number needed to  12 treat, I think there's been some perhaps  13 misunderstanding of that.</p> <p>14 It was suggested that this was to  15 get the average 75th percentile patient out  16 early. But what's actually the number needed  17 to treat from the get-go, with an  18 intent-to-treat analysis to get the median  19 patient out 24 hours earlier?</p> <p>20 Did you understand my question?  21 DR. TECHNER: Sort of.  22 DR. BUCHMAN: Let me rephrase it then.</p>

254	<p>1 DR. TECHNER: Go ahead.</p> <p>2 DR. BUCHMAN: Simply, what is the</p> <p>3 number needed to treat? How many patients from</p> <p>4 an intent-to-treat analysis have to be given the</p> <p>5 medication in order to get a single patient out</p> <p>6 24 hours earlier, regardless of which percentile</p> <p>7 they fall into?</p> <p>8 DR. TECHNER: I think in order to</p> <p>9 answer your question, let's look at the</p> <p>10 responder analysis for discharge order written,</p> <p>11 and I believe that will provide a range of NNTs</p> <p>12 that you can use to judge. As you remember, we</p> <p>13 did do a responder analysis. And if you recall,</p> <p>14 that responder analysis was based on patients</p> <p>15 who achieved the endpoint of interest between</p> <p>16 any of Postsurgical Days 3 through 8, and then</p> <p>17 had no subsequent reports, adverse event reports</p> <p>18 of ileus, that either led to prolonged</p> <p>19 hospitalization or readmission within seven days</p> <p>20 of discharge.</p> <p>21 No, sorry. Wrong slide. Why don't</p> <p>22 you go back to my core slide? Percentage of</p>	256	<p>1 per year even if it's used strictly on-label,</p> <p>2 I'm wondering whether you think a safety</p> <p>3 database and POI of about 2,600 patients is</p> <p>4 adequate to address the safety signal of MI?</p> <p>5 DR. JACKSON: Dr. Alexander, may I ask</p> <p>6 you if you would respond to that question for</p> <p>7 Dr. Hennessy?</p> <p>8 DR. ALEXANDER: John Alexander from</p> <p>9 Duke University. The patient population that's</p> <p>10 enrolled in these clinical studies, and in fact,</p> <p>11 the patient population that undergoes elective</p> <p>12 bowel resection surgery is at generally</p> <p>13 relatively low risk for cardiovascular events.</p> <p>14 And so the perioperative myocardial infarction</p> <p>15 rate in this population is likely to be less</p> <p>16 than 1 percent.</p> <p>17 So even enrolling substantially</p> <p>18 larger numbers of patients on the orders of</p> <p>19 10- to 20,000 in a safety database is</p> <p>20 unlikely to eliminate or exclude modest</p> <p>21 increases -- 25, 50 percent increases -- in</p> <p>22 myocardial infarction with alvimopan. So</p>
255	<p>1 patients discharged by Postsurgical Day 7. I</p> <p>2 think that's what I was looking for; I'm</p> <p>3 sorry. Yes.</p> <p>4 So I think when we look across the</p> <p>5 studies, using that responder definition I</p> <p>6 just defined, we can see here that the NNTs</p> <p>7 to get patients out, in the pooled data for</p> <p>8 bowel resection only, within seven days</p> <p>9 ranged from five to nine. And this is across</p> <p>10 each of the individual trials. And so this</p> <p>11 is looking at responders in the pooled data</p> <p>12 from each individual study. And I think what</p> <p>13 you can see, one, is a higher proportion of</p> <p>14 alvimopan responders. And when you look at</p> <p>15 the absolute difference between these in each</p> <p>16 study, the NNTs you get are between five and</p> <p>17 nine.</p> <p>18 DR. BUCHMAN: Dr. Hennessy?</p> <p>19 DR. HENNESSY: Thank you. Given that</p> <p>20 alvimopan, at least as far as we know, doesn't</p> <p>21 save any lives, and given that the size of the</p> <p>22 potential market is at least 400,000 patients</p>	257	<p>1 with rare cardiovascular or other safety</p> <p>2 events, there's a real challenge in low-risk</p> <p>3 populations of excluding them, even with</p> <p>4 large safety databases.</p> <p>5 In the totality of evidence from</p> <p>6 the POI population studies, and the analyses</p> <p>7 that we've gone over quite extensively from</p> <p>8 the OBD populations, there's risk, there's</p> <p>9 possible risk, increased risk of myocardial</p> <p>10 infarction that showed up in one OBD</p> <p>11 population study that -- where there was no</p> <p>12 such signal for MI or any other rare event in</p> <p>13 the POI studies or in the other OBD studies.</p> <p>14 DR. BUCHMAN: Dr. Epstein?</p> <p>15 DR. EPSTEIN: Yes, question for</p> <p>16 Dr. Techner. Dr. Epstein from Annapolis. Could</p> <p>17 we go back to slide CA 31? In this pooled study</p> <p>18 or, for that matter, in 314, for example, did</p> <p>19 you get a chance to look at the different age</p> <p>20 brackets by decade? Perhaps to see if -- you</p> <p>21 know, elderly patients obviously are less mobile</p> <p>22 and they may have more of an ileus, so your</p>

<p style="text-align: right;">258</p> <p>1 effect may be greater in that population. I'm  2 just wondering if you had a chance to look at  3 that group and see if there was any clinical  4 difference maybe by decade.  5 DR. TECHNER: We did, and it brings up  6 I think a very interesting point. So we broke  7 down the population for you here. This is  8 looking at GI-2 by age in the pooled North  9 American trials: Less than 65 years, greater  10 than or equal to 65 years, and greater than or  11 equal to 75 years. I think what you can see  12 here is that regardless of where we cut the age  13 group, we see consistent benefit throughout.  14 And yes, the numbers are not quite as large, but  15 we tend to see somewhat of a more robust  16 response in patients that are elderly.  17 DR. BUCHMAN: Dr. Pasricha?  18 DR. PASRICHA: I had a couple of  19 questions, one of them related to preclinical  20 data.  21 Do you have any preclinical data on  22 the effects of this drug on vascular tone?</p>	<p style="text-align: right;">260</p> <p>1 makes sense that what you'd really want to  2 reduce the time in are the patients in whom  3 there's a problem. So a patient who only stays  4 for one day, it doesn't matter as much whether  5 you reduce their time.  6 On the other hand, someone who  7 takes five or six days, maybe it's a lot more  8 important to reduce their time. And  9 likewise, if you went to the other extreme  10 and took people -- I know the maximum here is  11 only 10 days, but if you had data going out  12 to 30 days, then maybe a one-day difference  13 wouldn't be very important. So it seems to  14 me that the 75th percentile actually might be  15 fairly reasonable in terms of clinically  16 important. But this is coming from a  17 non-clinician.  18 And the other thing I wanted to ask  19 about was this decision about going to GI-2  20 instead of GI-3. You know, I'm worried that  21 that hindsight may have been driven by  22 results a little bit. And I'm wondering if</p>
<p style="text-align: right;">259</p> <p>1 Have you done isolated blood vessels and seen  2 if there's any change in vasomotor activity?  3 I know you looked at blood pressure in intact  4 animals. But have you specifically looked at  5 that, because that's one of the preclinical  6 screening tests for --  7 DR. JACKSON: Yes, I'm going to ask  8 Dr. Garver to address that preclinical question.  9 DR. GARVER: Deanne Garver, a  10 non-clinical consultant to Adolor. There have  11 been no systematic studies done for localization  12 of the mu-receptors in the cardiovascular  13 itself. There's some limited data with respect  14 to the distribution in heart, which is largely  15 kappa- and delta-receptors, and not the  16 mu-receptor.  17 DR. BUCHMAN: Dr. Proschan?  18 DR. PROSCHAN: Yeah, I'm a  19 statistician, so I'm trying to get the clinical  20 understanding in terms of the mean and the  21 median and so forth. And I'm thinking, from a  22 clinical standpoint, to me as a statistician, it</p>	<p style="text-align: right;">261</p> <p>1 you're so convinced that GI-2 is really the  2 better endpoint, then why did you decide on  3 GI-3 at the beginning of some of those  4 studies?  5 DR. TECHNER: You know, the clinical  6 development program for Entereg really spanned  7 almost seven years, a long seven years. And  8 we're still here. And I think, to be quite  9 frank with you, it's a learning experience. I  10 mean, we have to understand a couple of things.  11 One, there is no precedent here. There's no  12 guidance document to tell a sponsor how to  13 develop a drug to manage postoperative ileus in  14 patients undergoing bowel resection.  15 So in essence, Adolor and GSK kind  16 of were carving the path. And so we really  17 relied on I think two very important  18 things -- three important things. One, our  19 data as we accumulated it. Two, our  20 surgeons, our anesthesiologists, our  21 statisticians, our physicians who really  22 helped us understand the condition, and what</p>

<p style="text-align: right;">262</p> <p>1 really matters from their perspective and  2 from the patient's perspective. And third,  3 the FDA, who we've been collaborating with  4 over this entire period of time.  5 And I think when we looked at  6 everything, the data, what's important to the  7 surgeons, what's important to the patients,  8 what really gets to the treatment effect of  9 alvimopan, and our ability to really assess  10 that so that we can be able to give you data  11 that you feel confident in making your  12 decision, it really came down to GI-2. And  13 that really is the honest answer. It was a  14 learning experience. We took input from  15 everybody, and that's how we got there.  16 DR. BUCHMAN: Dr. Pasricha?  17 DR. PASRICHA: I just had a couple of  18 questions about the cancer signaling, because I  19 remain a little concerned about that.  20 Dr. Dannis mentioned that there was a fairly  21 large difference in the Karnofsky scores between  22 the two groups receiving the drug and the</p>	<p style="text-align: right;">264</p> <p>1 some information on two-year survival after  2 exposure, even though brief, to this drug. And  3 that should not be very difficult to get.  4 DR. MORTENSEN: Eric Mortensen, GSK.  5 Let me first speak to your direct question about  6 the multi-event analysis, and I'll ask us to put  7 that up.  8 Understandably, we wanted to know  9 why we were seeing this gross imbalance, the  10 20 versus 30 that we saw in the continuum of  11 008, 101, 684. And so in conjunction with  12 our external consultants, we suggested that  13 we had to consider that, given that we had  14 not made any effort, because that was not the  15 objective of the study, to try to balance  16 patient Z severity or prognostic factors,  17 that we should investigate some very  18 well -- clinically well-established  19 prognostic factors for death and disease  20 progression in patients to see whether or not  21 we really had balance between the treatment  22 groups.</p>
<p style="text-align: right;">263</p> <p>1 placebo in the OBD study; is that correct? And  2 if you correct for that variable, do you still  3 see a risk, an increased risk for cancer?  4 Because there's a question over this immune  5 surveillance may be related to that effect and  6 it's not truly a drug effect.  7 DR. BUCHMAN: Microphone, please?  8 DR. DANNIS: I'm not sure we looked  9 into that.  10 DR. PASRICHA: And the question of the  11 sponsor is, it's probably been at least two  12 years since you've completed the study or  13 enrolled your last patient in the study; is that  14 correct?  15 DR. JACKSON: No, 014, the data are  16 not quite as mature as that. And we did -- if  17 you'd like an answer from the sponsor to that  18 question, I think we can provide it.  19 DR. PASRICHA: What I would like to  20 see, especially since most of these patients  21 were treated for cancer, with this new  22 information on the signaling, I'd like to see</p>	<p style="text-align: right;">265</p> <p>1 Now, what I'm showing here, this  2 first, just looking at the initial unadjusted  3 hazard ratio for the risk of death in the  4 continuum of 008, 101, 684, and we see  5 there's a 2.1 alvimopan to placebo, again,  6 broad confidence in embracing one because  7 we're talking about small numbers here. The  8 next steps were then to look at the influence  9 of those factors that were thought to  10 potentially be related to what we saw as the  11 imbalance.  12 Again, we note we had a numerical  13 increase in the number of patients who had  14 with non-small cell lung cancer in the  15 alvimopan treatment group. And we saw here  16 that we ended up doing this in a sequential  17 step stages of looking at a multi-variant  18 model, and that actually showed the most  19 significant risk factor for patients' death.  20 So imbalances based upon their underlying  21 diagnosis would potentially significantly  22 impact the outcome of patients.</p>

<p style="text-align: right;">266</p> <p>1 But in addition, we also then  2 looked at two other factors. One is  3 Karnofsky score. Now, Karnofsky scores are a  4 patient performance score that is I guess  5 commonly used in many oncology studies. And  6 what we found is that each additional  7 10-point decrease in Karnofsky score is  8 associated with additional worsening of  9 patient's outcome and greater probability of  10 the patient being moribund.  11 And so we see that for each  12 10-point decrease, we then see a hazard ratio  13 increase of 1.5. And I'm emphasizing that  14 because it's not saying that it was an  15 arbitrary cut. Each cut, from 100 to 90 to  16 80, you're seeing each of those cuts, and if  17 you then have the increase in those patients  18 in the treatment group, a progressive  19 worsening of their outcome. And then, a  20 similar number of metastatic sites for their  21 cancers. And again, there's a numeric  22 increased number of patients with more</p>	<p style="text-align: right;">268</p> <p>1 the United States. A total of 85 percent of  2 the patients overall were from the United  3 States, Canada, and the U.K. We then also  4 had a small number of patients contributing  5 from other sites, fewer than 1 percent from  6 either Poland or Hungary.  7 And then we had fewer than  8 3 percent of patients coming from New  9 Zealand, Australia, Hong Kong, and Taiwan.  10 So it was largely a study conducted in the  11 U.S., Canada, and U.K.  12 DR. JACKSON: This is David Jackson,  13 Adolor. In regard to the second part of your  14 question, we do not have, obviously, two-year  15 follow-up on those patients. But we've talked  16 extensively about the IDMC and the consideration  17 of the cardiovascular effects of that drug.  18 Obviously, there was no place for an IDMC and  19 that the neoplastic findings were after the  20 study was finished.  21 We did, however, convene a panel of  22 expert oncologists, one of whom is present</p>
<p style="text-align: right;">267</p> <p>1 metastases, and that the treatment group,  2 that was also as you see here, seen to be  3 positively associated with an increased risk  4 for death.  5 So when we adjusted the studies for  6 the proportion of patients with these  7 differences between the alvimopan group  8 versus placebo, we actually saw that we had a  9 decrease in the adjusted hazard ratio to 1.4.  10 Again, with a wide confidence level, but at  11 least that gave us some confidence that the  12 factors that we were told by external experts  13 in oncology that might very well be  14 influencing the outcomes of our study seem to  15 be borne out.  16 I was going to give a quick factual  17 answer to the earlier question that was  18 asked. There was an earlier question about  19 the distribution of patients in 014, and I  20 just wanted to just very quickly get back to  21 that and answer your question. Briefly,  22 65 percent of the patients in 014 were from</p>	<p style="text-align: right;">269</p> <p>1 today, and would I'm sure be very happy to  2 provide his thoughts if you'd like to hear  3 them.  4 DR. FUCHS: Hi. I'm Charlie Fuchs,  5 medical oncologist and cancer epidemiologist at  6 the Dana-Farber Cancer Institute in Boston. And  7 our group did look at the evidence in its  8 totality to look at the relationship between  9 this drug and cancer risk, and thought about  10 sort of several of the major criteria that one  11 considers when thinking about cancer risk.  12 First, there really was not a  13 plausible biological mechanism by which this  14 opiate antagonist would contribute to cancer  15 risk. None that we're aware of. The  16 question was asked earlier about the presence  17 of mu-receptors on cancer cells. I'm not  18 aware of that. In fact, in terms of looking  19 at opiate antagonists and opiates on immune  20 surveillance, there is limited evidence, but  21 would suggest that opiates sometimes reduce  22 NK cell activity, whereas antagonists might</p>

<p style="text-align: right;">270</p> <p>1 increase it. Now, I think that's purely  2 speculative, but doesn't suggest that one  3 impairs immune surveillance. So bottom line  4 is, first, we didn't see clear biological  5 plausibility for a relationship with this  6 drug and cancer.  7       Secondly, as you've seen, the  8 genotoxic studies and the animal studies  9 delivered over two years failed to  10 demonstrate any clear carcinogenicity of the  11 compound.  12       Thirdly, the time course seems  13 implausible. Namely, the idea that cancers  14 could develop in a matter of weeks to months  15 is unlikely with any agents.  16       And then finally, the histology.  17 We're clearly looking at a panoply of cancer  18 histologies.  19       And when assigning risk, one  20 usually expects to see a specific tumor  21 histologic type. And as you saw in the data,  22 we're not seeing any clear pattern. So in</p>	<p style="text-align: right;">272</p> <p>1 given the potential complications however  2 minimal they be because we have to consider a  3 cost-benefit analysis. Do you think you should  4 be required to do a single dose, a preoperative  5 dosing study -- in other words, 6 or  6 12 milligrams one time only preoperatively as  7 the only dose, another study?  8       Do you think you should be required  9 to do that? And if not, why not?  10       DR. TECHNER: Before I answer your  11 question, I'd like to, if you don't mind, make  12 one point of clarification, because I think it  13 will help in you understanding the response.  14       DR. BUCHMAN: My question is  15 predicated on the answer to my previous  16 question, where you illustrated the continuous  17 difference between the curves at all points,  18 even as soon as two days postoperatively.  19       DR. TECHNER: Let me start by  20 clarifying something, and I think it was a point  21 actually that Dr. Chang raised, and also  22 Dr. Dannis.</p>
<p style="text-align: right;">271</p> <p>1 sum, we're really not seeing any convincing  2 evidence that would link alvimopan with  3 cancer risk.  4       Finally, with regard to the POI  5 indication, we're looking at seven days of  6 exposure to the drug, and I'm not aware of  7 any precedent where a drug that doesn't have  8 any genotoxicity or carcinogenicity would  9 lead to cancer risk with a seven-day  10 exposure.  11       DR. BUCHMAN: As chair, I'm going to  12 take the prerogative to ask the last question  13 for this session. Given that we're dealing with  14 a benign condition here, vis-a-vis I'm not aware  15 of a single case report of anyone dying from  16 postop ileus; furthermore, I'm not aware of any  17 data that would suggest that leaving hospital  18 hours earlier also decreases nosocomial  19 infections, C. diff, or anything else that we've  20 discussed, and you haven't shown that actually  21 in your study that you showed a positive benefit  22 there, we need to limit exposure to the drug</p>	<p style="text-align: right;">273</p> <p>1       And I think we -- and I think  2 Drs. Senagore and Delaney can speak better  3 than I to this, agree that virtually all of  4 these patients are being seen by their  5 surgeon within generally two to four weeks.  6 And actually, I can tell you that we polled  7 all of our sites, and the vast majority of  8 our surgeons see their patients back for  9 their first follow-up visit within two to  10 four weeks. Per all of the protocols, the  11 sites were required to report any serious  12 adverse events that occurred between the last  13 dose of study drug and 30 days following that  14 time point.  15       In addition, we had monitors  16 visiting these sites routinely, scouring  17 through the hospital records, the clinicians'  18 medical office records, and any other medical  19 records that were available, to ensure that  20 anything that looked like an adverse event  21 was captured. And the sites were instructed  22 to report any adverse events, including</p>

<p style="text-align: right;">274</p> <p>1 serious adverse events, that occurred during  2 that period of time. So we believe that the  3 database that FDA currently has would include  4 those events that occurred basically from the  5 onset of study through 30 days post last  6 dose. So I just wanted to clarify that to  7 give you a perspective of follow-up.  8 Dr. Schmith from GSK?  9 DR. SCHMITH: Hi, Ginny Schmith from  10 GSK. I wanted to comment on the idea that a  11 single dose preoperatively would work. And I  12 would argue that I do not believe that it would,  13 and I'd like to show you a plot as to why.  14 Dr. Techner had told us originally  15 that the time above the KI for the mu-opioid  16 receptor was longer with a 12-milligram dose  17 than with a 6-milligram dose. Okay? And  18 this data comes from POI patients. Okay. We  19 have collected samples in POI patients, and  20 they do have higher concentrations than we  21 would expect to see in healthy volunteers,  22 because they have higher viability because</p>	<p style="text-align: right;">276</p> <p>1 would be lost. And this is not that dissimilar  2 from administering antibiotics to prevent wound  3 infection, and other prophylactic measures that  4 we use in order to reduce the chance that a  5 patient will get a certain condition.  6 DR. BUCHMAN: That goes back to a  7 question I had a few hours ago. And that is, is  8 it what you're really treating here is not a  9 postop ileus at all, that you're treating  10 narcotic-induced ileus? I can tell you from  11 dealing with a lot of patients with complicated  12 GI surgery, those that stay the longest are  13 those that have a trigger finger. They can't  14 get their finger off of the PCA pump. And they  15 may stay a couple of weeks in the hospital with  16 a postop ileus. And so that also then brings up  17 the issue of using it more than seven days.  18 But the most important issue is,  19 are you seeking an indication that perhaps  20 doesn't truly exist or that you weren't  21 really treating? That you're treating a  22 completely different indication, being a</p>
<p style="text-align: right;">275</p> <p>1 they do have a decreased GI transit and more  2 time for the drug to be absorbed. Okay? But  3 as you can see, this is a over a 12-milligram  4 dose over a 12-hour period. So they're above  5 the KI for 12 hours. They're not going to be  6 above the KI for five days.  7 DR. BUCHMAN: But if you prevent the  8 development of a postop ileus, why would you  9 need to give it for five days? If you don't  10 have a postop ileus at Day 1, you're not going  11 to suddenly get one at Day 5.  12 DR. TECHNER: I will address that, and  13 I will also ask Dr. Senagore to address that as  14 well. I think we discussed the fact that ileus  15 is multifactorial. Opioids are definitely a key  16 component. So as long as a patient is receiving  17 opioids, the risk that ileus is prolonged is  18 high. And therefore, we believe that if you  19 only gave one dose preoperatively and the  20 patient continued to get opioids, then in  21 essence, that preoperative dose effect, the  22 chance to mitigate the effect of those opioids,</p>	<p style="text-align: right;">277</p> <p>1 narcotic-induced ileus.  2 DR. TECHNER: I think this is the way  3 I would respond to that. If the standard of  4 care in this country was to manage postoperative  5 pain with no narcotics, then I don't believe we  6 would feel this drug would have a benefit. I do  7 not believe that that is the standard of care  8 here.  9 DR. BUCHMAN: You can answer the other  10 question when we get to some of the questions.  11 Dr. Krist, you had one question. Then we've got  12 to move on to the questions.  13 DR. KRIST: Well, maybe my question is  14 better to be brought up as we address these  15 questions. What I'm really looking for is  16 reassurance that we don't need to be worrying  17 about looking at long-term safety issues for the  18 short-term indication of the medicine. And I  19 know we've been trying to talk about this, and  20 we've been skirting around that topic when we're  21 looking at the incidences of cancer and MI and  22 those types of things. But the picture that I</p>

278	280
<p>1 keep coming back to that has me uncomfortable is</p> <p>2 I hear consistent information about efficacy.</p> <p>3 The clinical significance, we could</p> <p>4 talk about, and as Alan, you brought up we</p> <p>5 don't see reductions in mortality and DVT and</p> <p>6 nosocomial infections, but we do see</p> <p>7 consistent reductions in nausea and postop</p> <p>8 ileus and earlier discharge from the</p> <p>9 hospital.</p> <p>10 But I also hear a drug that would</p> <p>11 apply to 400,000 people that you can't</p> <p>12 predict who's going to need it, so you've got</p> <p>13 to give it to everyone. It's something that</p> <p>14 I would envision a surgeon would just do.</p> <p>15 You wouldn't really discuss it with the</p> <p>16 patient, because there's bigger things to</p> <p>17 think about, like your cancer resection and</p> <p>18 other things like that that patients are</p> <p>19 dealing with. So I feel like there's a lot</p> <p>20 of importance for making sure that this is</p> <p>21 safe.</p> <p>22 And on one hand, I heard</p>	<p>1 reassurance and trying to figure out, well,</p> <p>2 why don't we need to worry about looking at</p> <p>3 that longer time period for the short-term</p> <p>4 administration? I know it wasn't the plan</p> <p>5 and it came up afterwards, after these spikes</p> <p>6 appeared. But before releasing a drug and</p> <p>7 saying it's safe and potentially exposing a</p> <p>8 lot of people to it, it seems like an</p> <p>9 important thing that we need to figure out.</p> <p>10 DR. BUCHMAN: So your question is if</p> <p>11 we use similar cumulative doses, why don't we</p> <p>12 look at the data the same? Is that the question</p> <p>13 that you're asking?</p> <p>14 DR. KRIST: The cumulative dose, I</p> <p>15 didn't mean to -- it's not an issue of the</p> <p>16 cumulative dose.</p> <p>17 It was more of an issue of on one</p> <p>18 hand, we're saying, well, if you give it</p> <p>19 short-term, in the studies we see, we don't</p> <p>20 see risks of MI in the POI studies. But as</p> <p>21 Sean was bringing out, we probably don't have</p> <p>22 power to see that at least short term.</p>
279	281
<p>1 Dr. Lincoff earlier say, well, why would a</p> <p>2 drug that you give for seven days cause an MI</p> <p>3 three to six months later. So we see these</p> <p>4 spikes in the folks on the long-term use of</p> <p>5 the medication. And I can buy that, but on</p> <p>6 some level, the people in the short term are</p> <p>7 getting more of the drug. They're getting</p> <p>8 120 to 168 milligrams, where the people on</p> <p>9 the long-term dose -- if you're looking 40</p> <p>10 days to 120 days out, they getting 40 to 120</p> <p>11 milligrams of the medicine.</p> <p>12 And then in the risk management</p> <p>13 plan, I don't see anything to even go back or</p> <p>14 look at or think about -- if you give it for</p> <p>15 a short period of time, are there these</p> <p>16 long-terms complications that we saw the</p> <p>17 spikes of? Cancer, I can buy more as a</p> <p>18 short-term dose. You can have an increase in</p> <p>19 cancer 6 to 12 months later. That certainly</p> <p>20 is plausible. MI, I have a more difficult</p> <p>21 time with.</p> <p>22 But I'm just looking for some</p>	<p>1 The thing I'm concerned about is</p> <p>2 our follow-up is 14 days, and the spikes in</p> <p>3 the chronic use folks occurred at 40 to 120</p> <p>4 days. The issue of the dose was just -- the</p> <p>5 positive towards the POI studies is, well,</p> <p>6 it's only five to seven days people get it as</p> <p>7 opposed to 60 to a year's worth of days that</p> <p>8 they get it. But the negative is the</p> <p>9 cumulative dose might be more in the</p> <p>10 short-term POI patients in the studies.</p> <p>11 DR. JACKSON: David Jackson from</p> <p>12 Adolor. I'd love to make you comfortable in</p> <p>13 that regard, obviously. In part, I'd like to</p> <p>14 answer your question with providing an answer to</p> <p>15 a comment that came from the left side of the</p> <p>16 committee table earlier. And I apologize, I</p> <p>17 can't remember whether it was Dr. Lincoff or</p> <p>18 Dr. Talamini. But the size of this acute care</p> <p>19 safety database at 4,000 patients is actually</p> <p>20 rather large for a short-term administered</p> <p>21 product. Okay?</p> <p>22 DR. KRIST: Short term.</p>

<p style="text-align: right;">282</p> <p>1 DR. JACKSON: So we have a lot of  2 data. The second point I would offer is that in  3 the OBD data, the risk, whatever it is, whatever  4 that signal, if it is a signal, means, is  5 largely confined to one single study. Those  6 other studies which looked at a significant  7 number of patients for three months did not see  8 that imbalance. So although we don't understand  9 perhaps the meaning of the signal right now, if  10 it is such, we have a preponderance of data in  11 which we don't see anything.</p> <p>12 DR. KRIST: But that one study was the  13 main one that followed people for a year. The  14 other one stopped at three months, right?</p> <p>15 DR. JACKSON: Yes, but the myocardial  16 infarctions were all seen in the first four  17 months.</p> <p>18 There was nothing seen at all in  19 the last six months of that study.</p> <p>20 DR. KRIST: Not necessarily true,  21 though, for the cancer risk, of course.</p> <p>22 DR. JACKSON: Absolutely not, but</p>	<p style="text-align: right;">284</p> <p>1 The first question is a non-voting  2 question, and we'll spend about 10 to 15  3 minutes on this, less if we need. And the  4 question is, for the record, for the  5 assessment of efficacy in clinical trials of  6 postoperative ileus, GI-2 and GI-3 have been  7 utilized to measure times for recovery of  8 upper and lower GI function.</p> <p>9 What do you consider a minimal  10 acceptable treatment difference as measured  11 by GI-1 or GI-3 for alvimopan relative to  12 placebo? Specifically, do you think 12 hours  13 is sufficient? Twenty-four hours, 36 hours,  14 a month, 12 years? We need your comments on  15 this.</p> <p>16 Dr. Pasricha?</p> <p>17 DR. PASRICHA: I just think we need to  18 clarify what time points or what percentile  19 we're talking about. Are we talking about the  20 means for the whole -- are we talking about  21 differences in means?</p> <p>22 DR. BUCHMAN: That's a good question</p>
<p style="text-align: right;">283</p> <p>1 again, as I think my colleague Dr. Mortensen  2 tried to indicate, there is a very good chance  3 that a large number of those cancers were  4 present at the time of introduction into the  5 study.</p> <p>6 DR. KRIST: Likewise, there's no  7 methodologic reason to say that we shouldn't be  8 considering Study 14. Even though it all  9 occurred in that one study, there's no -- when  10 you look at that study compared to the other  11 studies, there's no explanation as to why it  12 occurred in that one study compared to the  13 others.</p> <p>14 DR. JACKSON: There is indeed not, and  15 we have looked very hard for that.</p> <p>16 DR. BUCHMAN: Unfortunately, we're  17 going to have to move on and catch up here.  18 We're going to move on to the questions that the  19 agency has posed to the committee. Some of  20 these will be questions that the committee will  21 actually vote on, and I will announce those as  22 we get to them.</p>	<p style="text-align: right;">285</p> <p>1 here. Are we talking about the mean, median,  2 or 75th percentile?</p> <p>3 DR. KORVICK: I would think that  4 anyone that responds to this question should  5 specify what's the most meaningful to them, and  6 why and how much. So you can pick whichever one  7 you think is meaningful to you.</p> <p>8 DR. PASRICHA: So I'd like to say in  9 general that reducing postop stay by 24 hours on  10 an average patient is meaningful. But if you're  11 talking about an operation or a procedure that  12 results only in 3 days hospitalization and you  13 can reduce that by 12 hours, that might be  14 meaningful, also. So in part, it depends on the  15 denominator, which is one of the reasons we  16 asked the question. But if you just take sort  17 of this dumb average that we have, five days and  18 so on, I think 24 hours would be considered a  19 meaningful endpoint.</p> <p>20 DR. BUCHMAN: Dr. Talamini?</p> <p>21 DR. TALAMINI: I would say as one of  22 those surgeons on the committee who's watched</p>

286	<p>1 lots of patients go through this, I think for  2 me, 12 hours in terms of the GI-2 endpoint or 12  3 hours in terms of being able to leave the  4 hospital would be significant.  5 I'd like to add one quick comment  6 to follow up on what you said, Dr. Buchman.  7 The surgeons in the room know when we finish  8 most operations, the small bowel is  9 peristaltic. So there is this definition.  10 You know, in our minds, we have this ileus  11 thing when we close a patient. When we close  12 a patient, the small bowel's functional. The  13 colon usually isn't, the stomach usually  14 isn't, but the small bowel is. It'd be  15 fascinating to know by ultrasound what's  16 really going on with the bowel at all these  17 time points, but we don't.  18 DR. BUCHMAN: Dr. Levine?  19 Dr. Epstein?  20 DR. EPSTEIN: Yes, just to expand a  21 little bit on what Dr. Talamini said. And as  22 we've been going through this discussion and</p>	288	<p>1 had a bowel resection, if you could save one  2 hospital bed day or even half a bed day,  3 which is significant, or 12 hours, you're  4 talking about 55 bed days. That's very  5 substantial. It's not only you're getting  6 the patient out of the hospital early and  7 saving money, but you're putting somebody in  8 the hospital on that day and you're able to  9 do more surgeries.  10 I don't know about the hospitals or  11 the places where everyone else works, but we  12 have a very, very critical bed shortage on a  13 daily basis. And this is a common problem  14 throughout our area. So this would have a  15 significant pharmacoeconomic impact if we  16 could save even 12 hours on our postoperative  17 patients. So from that standpoint, I think  18 this drug would be very beneficial if we  19 could make that change in our time of stay.  20 DR. BUCHMAN: Dr. Talamini and  21 Dr. Epstein, if the nurse called you at home,  22 and actually both of you are probably rounding</p>
287	<p>1 talking a lot about the safety, we've also gone,  2 and Dr. Chang has made the comments, on more of  3 a pharmacoeconomic argument, which is kind of  4 unique in my experience on panels. But  5 nevertheless, it's an important thing to  6 discuss. And just by way of my background, I've  7 served as president of a medical staff and on a  8 board of a 700-physician hospital for more than  9 a decade. So we wrestle with these issues from  10 the pharmacoeconomic every day. And we also  11 have the P&amp;T committee, which would then  12 consider this drug because it's going to be a  13 hospital drug.  14 And a lot of our time is spent  15 trying to get the hospital bed days -- our  16 mean hospital bed days are around 3.16 days,  17 trying to get it from 3.23 days down to 3.16  18 days, and that is a huge number. It has  19 everything to do with reimbursement to the  20 hospital, quality indicators, and on and on.  21 And even if you look at this drug,  22 if you gave it to the 500 patients or so that</p>	289	<p>1 at midnight, and the patient eats dinner, solid  2 food -- and of course, we don't know what solid  3 food tolerance means. They ate a hot dog, they  4 ate a whole sandwich, they ate one piece of  5 toast. But if they call you at midnight and  6 say, well, the patient ate, can they go home  7 now, but the patient's asleep now, would you  8 send them home or would you wait until 8:00 in  9 the morning? And so basically that's just a  10 joke that didn't go over very well to illustrate  11 my point, does 12 hours really make a difference  12 clinically?  13 DR. TALAMINI: This is Dr. Talamini  14 again. I believe that it does, because most  15 surgeons, at least academic surgeons, which is  16 what I've been and lived with, really think of  17 these things twice a day: Once for the morning  18 and once for the evening. So if you hear from  19 the house staff in the afternoon bowels are  20 moving, patient's eating a diet, you'll say go  21 on home, and we'll have a bed fresh early the  22 next morning.</p>

290	<p>1 DR. EPSTEIN: Just to --</p> <p>2 DR. BUCHMAN: Dr. Krist?</p> <p>3 DR. EPSTEIN: I'm sorry.</p> <p>4 DR. BUCHMAN: Oh, I'm sorry,</p> <p>5 Dr. Epstein.</p> <p>6 DR. EPSTEIN: Just to reiterate on</p> <p>7 that. The protocol that we have in place in our</p> <p>8 hospital is we have a 24-hour team in the</p> <p>9 hospital, a discharge team. We have cars</p> <p>10 standing by ready to get you out of the</p> <p>11 hospital. It does not matter if it's New</p> <p>12 Year's, Christmas Eve, a blizzard.</p> <p>13 Our ER is -- we just built a</p> <p>14 brand-new hospital and our ER is stacked up</p> <p>15 with people in the hallways down the halls.</p> <p>16 We don't have room for these people, and it's</p> <p>17 really a troubling situation. But the point</p> <p>18 is that every hour makes a difference. And</p> <p>19 we can't even transfer a patient to another</p> <p>20 hospital. We have the same problem</p> <p>21 throughout the metropolitan area. So yeah,</p> <p>22 it's a big difference, and 12 hours is</p>	292	<p>1 So that's how I might rationalize and</p> <p>2 interpret the overall population mean versus</p> <p>3 the 75th percentile.</p> <p>4 DR. BUCHMAN: And of course, we saw a</p> <p>5 mean of six to seven hours in this study. So</p> <p>6 okay, well, we're going to move on to Question</p> <p>7 No. 2.</p> <p>8 DR. PASRICHA: The mean was about 15</p> <p>9 or something.</p> <p>10 DR. KRIST: The 75th percentile mean</p> <p>11 was closer to a day.</p> <p>12 DR. BUCHMAN: Were you referring to</p> <p>13 the overall mean or the mean for the 75th</p> <p>14 percentile?</p> <p>15 DR. KRIST: Well, the overall mean was</p> <p>16 more like 15 hours.</p> <p>17 DR. BUCHMAN: Fifteen. Fifteen,</p> <p>18 you're correct.</p> <p>19 DR. KRIST: And the 75th percentile</p> <p>20 one was 24 hours.</p> <p>21 DR. BUCHMAN: Yep, you're correct.</p> <p>22 We're going to move on to Question No. 2. And</p>
291	<p>1 enormous.</p> <p>2 DR. BUCHMAN: Dr. Krist?</p> <p>3 DR. KRIST: Now, I practice more at a</p> <p>4 community hospital, and I'm not sure that things</p> <p>5 happen in anything other than 24-hour</p> <p>6 increments, even though people want it to do,</p> <p>7 and we have bed shortages as well. But maybe</p> <p>8 this is where it helps us a little in thinking</p> <p>9 about whether we're talking about the mean or</p> <p>10 the 75th percentile. Because really, as you</p> <p>11 were talking earlier, for an individual patient,</p> <p>12 I think what's more clinically significant is</p> <p>13 24-hour increments. But if you're talking about</p> <p>14 mean for the overall group of patients who had</p> <p>15 the surgery, maybe 12 hours for that mean would</p> <p>16 be important, because that represents people who</p> <p>17 are getting out one or two days as well as</p> <p>18 people who are getting out an hour or two.</p> <p>19 Whereas if I look at the 75th</p> <p>20 percentile, more of the extreme of the people</p> <p>21 staying longer, maybe I want that to be more</p> <p>22 around 24 hours as opposed to the 12 hours.</p>	293	<p>1 keep in mind Question No. 2 is actually a voting</p> <p>2 question, and we'll have up to 30 minutes to</p> <p>3 discuss this. The question is, do you consider</p> <p>4 the efficacy results from the submitted POI</p> <p>5 studies to be clinically meaningful, and explain</p> <p>6 which of the endpoints, that's GI-1 -- or GI-2,</p> <p>7 GI-3, date of writing the order for discharge,</p> <p>8 or ready for discharge, or perhaps some other</p> <p>9 outcome that you feel is important? And which</p> <p>10 studies are you relying on to support your</p> <p>11 conclusion?</p> <p>12 Comments from the committee?</p> <p>13 Dr. Kramer?</p> <p>14 DR. KRAMER: I think before we</p> <p>15 actually discuss this, we should get to the</p> <p>16 question that you raised about what the actual</p> <p>17 indication is here. Because what bothers me in</p> <p>18 terms of determining efficacy is that</p> <p>19 essentially you have a situation where this drug</p> <p>20 has been shown to be effective when you required</p> <p>21 opioid patient-controlled analgesia. And if I</p> <p>22 got it right, I think when the surgeon,</p>

294	<p>1 Dr. Senagore, described the care pathways being  2 instituted across the country now, some of the  3 newer approaches, I think one of the things you  4 listed in general, not in these studies,  5 included opioid-sparing techniques. That was  6 excluded from these studies, with the exception  7 of the one in Europe.</p> <p>8 So in order to determine whether or  9 not this is efficacious, we have to say what  10 are we really doing? Are we minimizing the  11 effect of opioids, and should it have that  12 indication? Should it be tied to use in a  13 situation where you're administering PCA? So  14 you interpret the results accordingly. So  15 that's the comment I want to make.</p> <p>16 DR. BUCHMAN: Dr. Pasricha?  17 DR. PASRICHA: I think it's very hard  18 to look at the data and tease out what's  19 opioid-induced and what's non-opioid-induced in  20 the setting of postoperative ileus. So I'm not  21 sure that clinically that would be very helpful  22 for us to do that. I think you can clarify the</p>	296	<p>1 when you integrate across all time points, it  2 seems to me that 18 hours is pretty long as  3 well. So once again, from a non-clinician  4 standpoint, it seems like the results are  5 pretty good.</p> <p>6 DR. BUCHMAN: Dr. Rosing, do you have  7 any comments on this particular question?  8 Dr. Cullen?  9 DR. CULLEN: I think the results are  10 efficacious. I think that the GI-1-2 study and  11 the DOW as mentioned previously are what I look  12 at. And I think getting a patient out in a day  13 at 75th percentile is really significant.</p> <p>14 DR. BUCHMAN: Dr. Krist, anything to  15 add to your previous comments?  16 Dr. Levine?  17 DR. LEVINE: I just want to ask  18 Dr. Cullen, we agreed that in the 302 and some  19 of the other studies where we had total  20 abdominal hysterectomies, that this was going to  21 only look at postoperative ileus, not in the  22 gynecological surgery. On the other hand, if</p>
295	<p>1 context in which you're asking for efficacy,  2 which is I guess the context in which they're  3 asking for the label.</p> <p>4 And in my opinion, I think it is  5 clinically meaningful, the data. And I'm  6 relying on the GI-2 and the DOW endpoints to  7 support that. And I think we see it in all  8 the studies that have been presented.</p> <p>9 DR. BUCHMAN: Dr. Proschan?  10 MR. PROSCHAN: I just wanted  11 to -- actually, Slide CA 37 shows that the mean  12 difference is more like 18 hours. Now again, I  13 don't -- you know, I'm not a clinician, so I'm  14 probably the wrong one to be commenting on this.  15 But it seems to me that it's appropriate that as  16 you go out to the 75th percentile, you're  17 getting a bigger difference, a whole day; as  18 you're down in the lower amounts of time, maybe  19 12 hours is really important.</p> <p>20 You know, if you're talking about  21 the difference between three days and two and  22 a half, that may be very important. And then</p>	297	<p>1 you can save a half a day or a day in total  2 abdominal hysterectomy, it may be  3 cost-effective. My question is, can we  4 guesstimate if this would be utilized on or  5 off -- in the hospital on- or off-label by  6 gynecological surgeons for cancer surgery, where  7 there's total abdominal hysterectomy, when we  8 don't have data in that area shown in the  9 presentation?</p> <p>10 DR. BUCHMAN: Ms. Corkery-DeLuca, any  11 comments?  12 MS. CORKERY-DeLUCA: I haven't heard  13 enough negative to think --  14 DR. BUCHMAN: Use your microphone,  15 please.  16 MS. CORKERY-DeLUCA: Pardon me. I  17 haven't heard enough negative comments to say  18 that it would not be.  19 DR. BUCHMAN: Dr. Richardson?  20 DR. RICHARDSON: Richardson, Mayo. I  21 have a comment, and perhaps Dr. Talamini and  22 some of the other surgeons can answer this for</p>

298	<p>1 me. I know that at our institution, more and 2 more bowel resections are being done 3 laparoscopically, and that has shortened up the 4 stay substantially. And I guess I'm wondering, 5 if you're looking for this narrower indication, 6 that is using this particular drug only in the 7 situation of the open laparotomy, is this going 8 to be relevant as practice evolves? 9 DR. BUCHMAN: Dr. Chang? 10 Dr. Talamini, go ahead. 11 DR. TALAMINI: Should I respond? 12 DR. BUCHMAN: Go ahead. But this is 13 going to be your one time to respond, so make it 14 a full one. 15 DR. TALAMINI: I think that the data's 16 pretty clear that right now the majority are 17 open surgery. I think over time, though, those 18 numbers will shift and it's an unanswered 19 question. 20 I would say in terms of my 21 answering of Question No. 2, the endpoints 22 that are key to me are GI-2 and Ready,</p>	300	<p>1 that this is in the context of opioid PCA. 2 DR. BUCHMAN: I'd have to say who am I 3 to question the surgeon's judgment when to send 4 their patient home, although I don't 5 infrequently do that. 6 If I was the patient at 4:00 a.m., 7 and you're going to send me home, I'd beg you 8 to not wake me up first, and secondly, to 9 wait until 8:00 a.m. But given that there is 10 a feeling around the table from our surgeons 11 that 12 hours is clinically important for 12 ready for discharge, then I would have to say 13 I think that that is efficacious as well. 14 The problem with the written order 15 for discharge is it suffers from exactly the 16 same problems as actually going home, because 17 it's a red flag for insurance companies. If 18 I know a patient from out of state, for 19 example, is ready to go home on Friday and 20 they can't get picked up until Monday, I'm 21 not going to write that order. So it suffers 22 from exactly the same problems. So ready to</p>
299	<p>1 because GI-3, flatus, patients just can't 2 explain most of the time, and discharge order 3 depends on another human being in the chain. 4 So those are the data points that are 5 important. And I think that this is 6 significant based on those endpoints. 7 DR. BUCHMAN: Dr. Chang? 8 DR. CHANG: I would say I like what 9 Dr. Krist said about the mean being 12 hours and 10 at the 75th percentile, it's 24 hours. But I 11 would go by GI-2 because it is objective. I 12 don't feel like Ready or discharge 13 orders -- that's more subjective and it's based 14 on -- it could be variable. But obviously, the 15 results support the GI-2 endpoint, so I 16 definitely think this is efficacious. 17 DR. KRAMER: I'd like to say that I do 18 think that it's efficacious for -- I agree that 19 GI-2 makes sense, although it does bother me 20 that it looks like it was a post hoc decision 21 after the data was looked at, but it does make 22 sense. But I think the statement must specify</p>	301	<p>1 discharge is important. We're talking about 2 a benign condition, but if we can get the 3 patient out earlier and basically save 4 money -- that's the only thing we're talking 5 about here is potentially saving 6 money -- then I'm going to concur with my 7 surgical colleagues. 8 Dr. Hennessy? 9 MR. HENNESSY: Thanks. I would say 10 that the endpoint is clinically meaningful, but 11 only marginally so. It's right at the cusp. 12 DR. LINCOFF: As a non-GI specialist, 13 I would say that I think this endpoint is very 14 clinically meaningful from other conditions. A 15 day in the hospital or a half a day in the 16 hospital, I think is relevant, particularly a 17 day or a half a day of having an unpleasant 18 condition, like an NG tube or nausea. So from 19 that standpoint, I think that even a half a day 20 would be clinically relevant. 21 In terms of the endpoints, I think 22 that the GI-2 is the hardest endpoint, in</p>

302	<p>1 that it's most linked to an objective  2 finding. But I also believe that the DOW and  3 Ready are very important as well, in  4 particular because they're concordant with  5 the more mechanistic endpoint, and because  6 this is a blinded trial.</p> <p>7 So for all the limitation -- these  8 are blinded trials. So for all the  9 limitations inherent in the physician's  10 decision of when he's going to discharge and  11 if he's got people wandering around at night  12 ready to kick people out into the cars or  13 not, but whatever these are, they apply to  14 both groups, and they model clinical  15 practice. So for the very question of  16 relevance, where GI-2 is science, DOW and  17 Ready are clinical relevance and relevance in  18 medical practice. And so I think they're all  19 meaningful. They all support each other.</p> <p>20 And I think together it's a  21 very -- as much as I hate to use this  22 overused word -- robust findings, set of</p>	304	<p>1 voting procedure is going to go is I'm going to  2 read the question for the record, but then all  3 committee members who are going to vote yes, I'm  4 going to ask them to raise their hand. Now,  5 unfortunately, you're going to need to keep your  6 hand up in the air until Dr. Phan has recognized  7 that she has recorded your vote.</p> <p>8 Separately, we will then -- I will  9 then ask for those that are voting no, and  10 finally, those who abstain. And remember to  11 keep your hand up until it's acknowledged.  12 Not quite the secret ballot that we're used  13 to.</p> <p>14 So the question again is do you  15 consider the efficacy results from the  16 submitted POI studies to be clinically  17 meaningful? All those that say yes,  18 please -- I'm sorry, we have an interruption.</p> <p>19 DR. KRAMER: Can I just ask a  20 clarification?</p> <p>21 DR. BUCHMAN: Yes.</p> <p>22 DR. KRAMER: Can we specify that</p>
303	<p>1 findings, that there is efficacy for this  2 drug.</p> <p>3 DR. BUCHMAN: Dr. Epstein?</p> <p>4 DR. EPSTEIN: Yes, I agree with my  5 colleagues so far. And even just modeling  6 Dr. Talamini's hospital, the number of surgeries  7 he does, if you apply some numbers to this, it's  8 a very substantial clinical savings, cost  9 savings, time savings, that would outweigh any  10 cost of the medicine and its delivery.</p> <p>11 DR. BUCHMAN: Dr. Talamini had his  12 chance, but he begs me for one more. We have  13 time, so go ahead, Dr. Talamini.</p> <p>14 DR. TALAMINI: The only thing that I  15 would add to the differentiation that you're  16 bringing up, Dr. Buchman, is having personally  17 had a PCA after a very painful operation, it is  18 the Rolls Royce of pain control. And if this  19 does ameliorate or make that easier to use, I  20 think that's a consideration.</p> <p>21 DR. BUCHMAN: We're actually now going  22 to vote on this as a committee. And the way the</p>	305	<p>1 this -- since all the studies require PCA, that  2 this is the setting in which we're making the  3 statement?</p> <p>4 DR. BUCHMAN: Well, I think you can  5 make a comment, but as far as voting goes, the  6 question stands as is. You can certainly  7 abstain if you feel that it's an incomplete  8 question.</p> <p>9 Any comments from the agency?  10 Would they like to see that any differently?</p> <p>11 DR. KORVICK: I agree with what you  12 just said.</p> <p>13 DR. BUCHMAN: So all of those that  14 feel that the efficacy is clinically meaningful,  15 please raise your hand. Oh, please -- now that  16 you have your hand up, that was just an  17 exercise. Now you have to actually state your  18 name and say yes. And we're going to start with  19 Dr. Talamini.</p> <p>20 DR. TALAMINI: Talamini, yes.</p> <p>21 DR. EPSTEIN: Epstein, yes.</p> <p>22 DR. BUCHMAN: And you can put your</p>

306	308
<p>1 arms down. The war's over after you've voted.  2 DR. LINCOFF: Lincoff, yes.  3 MR. HENNESSY: Hennessy, yes.  4 DR. BUCHMAN: Buchman, yes.  5 DR. CHANG: Chang, yes.  6 DR. BUCHMAN: Losing hands over here.  7 Put them down after you've been recorded.  8 MS. CORKERY-DeLUCA: DeLuca, yes.  9 DR. LEVINE: Levine, yes.  10 DR. PASRICHA: Pasricha, yes.  11 MR. PROSCHAN: Proschan, yes.  12 DR. KRAMER: Krist, yes.  13 DR. CULLEN: Cullen, yes.  14 DR. ROSING: Rosing, yes.  15 DR. BUCHMAN: All those that vote no,  16 that the efficacy has not been shown, please  17 raise your hand. All those who are abstaining?  18 Please state your name.  19 DR. RICHARDSON: Richardson,  20 abstention.  21 DR. KRAMER: Kramer, abstention.  22 DR. BUCHMAN: With that, we're going</p>	<p>1 I think that a meaningful signal for  2 cardiovascular events, and in particular MI, was  3 raised for other studies. I think that the  4 studies in postoperative ileus were too small to  5 address that. I think there's a potential  6 mechanism underlying the potential signal, and  7 that is mu-opioid agonism can reduce  8 arrhythmias, so blockage would reduce that  9 reduction of arrhythmias. Given the number of  10 patients that are likely to see this drug, I  11 don't think that that safety signal has been  12 adequately addressed.  13 DR. BUCHMAN: Dr. Proschan?  14 MR. PROSCHAN: Yes, I also had  15 concerns. I was -- you know, for me, the two  16 big questions are, is 014 really different than  17 the others? And is the OBD different from POI?  18 And when I look at -- I did my own statistical  19 test to see if the results were different in 014  20 compared to the other trials, and I got  21 something that was statistically significant,  22 showing that there's a difference between 014</p>
307	309
<p>1 to --  2 MS. PHAN: So we have 13 yes, no nos,  3 and 2 abstains.  4 DR. BUCHMAN: Thank you, Dr. Phan.  5 With that, we're going to move on to Question  6 No. 3, which is a non-voting question. The  7 question is: based on currently available data,  8 do you have concern for the use of alvimopan  9 12-milligram capsules in the short term, that is  10 seven days or 15 doses, for the patient  11 following a partial large or small bowel  12 resection with primary anastomosis with regard  13 to the following: Cardiovascular events,  14 neoplastic events, and/or bone fractures?  15 If you noticed I only call on  16 anybody, put them in the hot seat if it's a  17 voting question, so this is a free-for-all  18 here.  19 If you have a comment, please make  20 it. Dr. Hennessy?  21 MR. HENNESSY: So yes, I do have  22 concerns with regard to cardiovascular events.</p>	<p>1 and the other OBD trials. Now, I don't know why  2 that is, so it's hard for me to dismiss GSK014,  3 because that's the one that had most of the MIs.  4 You're taking a trial that had more  5 of the information and trying to dismiss  6 that. I have a real problem with that. In  7 particular, you're estimating the odds ratio  8 better in that trial than you are in all of  9 the other trials in terms of variability.  10 The other thing that bothered me  11 was that it wasn't just MI. If you look in  12 014 in the briefing document, it looked like  13 it was arrhythmias, it looked like it was  14 other cardiac events. So that, to me,  15 suggests that this is not really just a  16 chance finding, those two factors.  17 As far as POI versus OBD, I did my  18 own statistical test and I did not get a  19 statistically significant difference in the  20 odds ratios for those two classes of trials.  21 And so that suggests that maybe the harm, if  22 you believe that there's harm, in OBD might</p>

<p style="text-align: right;">310</p> <p>1 also apply to POI, and we just don't have  2 enough events to detect that. So I did have  3 those concerns.  4 DR. BUCHMAN: Dr. Talamini?  5 DR. TALAMINI: I would say that I have  6 concerns. I don't have concerns regarding bone  7 fractures. I don't think I have concerns about  8 the neoplastic events, because looking at each  9 individual case, they're all over the board, and  10 many of them really just make no sense to me in  11 terms of long-term use of the drug in that  12 study.  13 I do have concerns about  14 cardiovascular events, which I think are  15 somewhat allayed by the comments here today  16 that nobody can point to a short-term drug  17 like this creating a longer-term  18 cardiovascular event. So I have concerns,  19 but I think they've largely been addressed.  20 DR. BUCHMAN: Dr. Kramer?  21 DR. KRAMER: I do have concerns, in  22 particular about the cardiovascular events. And</p>	<p style="text-align: right;">312</p> <p>1 time these patients were observed, a large  2 percentage of the patients were observed. So  3 I don't think we have adequate information to  4 say that there's even no relatively  5 short-term problem in the POI population.  6 So I do have a concern, and I think  7 that given that this benefit -- it's really  8 striking. The FDA is not allowed to make  9 decisions based on financial information or  10 cost savings, but now our clinicians are  11 making those decisions based on saving  12 hospitals money.  13 But our patients are being asked to  14 take this drug, I suspect without, as  15 Dr. Krist said, I suspect without a lot of  16 informed consent about what the potential  17 downsides are. Everyone has acknowledged  18 that it's really for those patients who are  19 going to have a problem. But since we don't  20 know who they are, all the patients have to  21 take it. That's when you get into trouble  22 later on, retrospectively, if you do discover</p>
<p style="text-align: right;">311</p> <p>1 it's not just short-term exposure causing  2 long-term effects, but I would say that the  3 follow-up in the short term was really  4 inadequate. Granted, at the time these studies  5 were done, it was not known that there was a  6 signal -- a signal would later show up in this  7 OBD population. But I think we have to keep in  8 mind that this was passive adverse event  9 reporting, and we know how doctors collect that  10 information. It's not an active solicitation of  11 cardiac events.  12 But furthermore, a very large  13 percentage of these patients were not  14 followed when they left the hospital, that  15 there's -- if I read the slide correctly, I  16 think it was 257 patients did not have any  17 further information. And that is not even  18 short-term follow-up. I mean, they could  19 have had an event at 10 days or 2 weeks. And  20 my understanding, even though the metabolite  21 is less potent than the parent drug, that the  22 metabolite would have been present past the</p>	<p style="text-align: right;">313</p> <p>1 the signal is real, that you have mud on your  2 face or egg on your face, however you want to  3 say it. So I have a concern.  4 DR. BUCHMAN: I had some concern as  5 well in terms of the long-term data. I don't  6 think we can ignore the long-term data, because  7 if we look at corticosteroids, for example,  8 well, you say seven days' worth of  9 corticosteroids, there's no increased risk of  10 bone fractures, but with cumulative use, there  11 certainly is. And it's the cumulative dose of  12 corticosteroids that have the greatest effect on  13 the risk of fracture.  14 So if we look at the long-term  15 data, the cumulative dose that those patients  16 have at a very small dose, but for a long  17 period of time, is very similar to the much  18 larger dose used for a very short period of  19 time. And indeed, it may be -- we don't know  20 this, but it may be the cumulative dose is  21 what's most important. Because many of these  22 patients that have an operation will be</p>

<p style="text-align: right;">314</p> <p>1 re-operated on in the future, and do they get  2 the medication again or are they allowed it  3 once in a lifetime?  4       If we look at a Crohn's patient,  5 for example, within five years of having a  6 strictureplasty, they've got a 40 percent  7 risk of being back in an operation again.  8 Patients who -- an ideal obviously with IBD  9 patients, but patients who have had an IPAA,  10 within five years have a greater than  11 50 percent chance of being in an operation  12 again because of a bowel obstruction from  13 adhesions. And do they then get this  14 medication again? Patients who have had 30  15 abdominal surgeries, they get 30 weeks of  16 this medication, that may prove to be a  17 significant risk. We don't have the  18 information on that, obviously.  19       Dr. Pasricha?  20       DR. PASRICHA: I think everybody on  21 this panel has some degree of concern about the  22 cardiovascular risks. The question is what do</p>	<p style="text-align: right;">316</p> <p>1 Dr. Lincoff couldn't think of any mechanisms  2 to cause long-term myocardial infarction, I  3 can't think of any reason once they're off  4 the drug that these people should be having  5 arrhythmias from a drug that's given over a  6 very short period of time. So we're really  7 talking about this concern about  8 cardiovascular problems on the basis of this  9 014 study, which seems to me to have a lot of  10 problems associated with it and doesn't make  11 a whole lot of sense from a cardiology  12 standpoint.  13       You raised the question,  14 Dr. Buchman, of the cumulative effect, but  15 even that breaks down, because once you get  16 out beyond 60 or 70 days, there was no  17 cumulative effect. That curve was perfectly  18 flat. So it seems to be an isolated effect  19 in a very brief period of time. There is  20 probably -- and it doesn't even reach  21 statistical significance apparently.  22       I think there's information we</p>
<p style="text-align: right;">315</p> <p>1 we do about them? And we have three options:  2 We either don't let this drug come on the market  3 or we do prospective trials, which you've  4 already heard are going to require tens of  5 thousands of patients and probably not answer  6 the question; or we put in place a very strict  7 risk management surveillance program, which are  8 really the three options that we have here. I  9 think a priori, we cannot necessarily come to  10 any conclusion about how severe the risk is  11 going to be based on the data we have.  12       DR. BUCHMAN: Dr. Rosing?  13       DR. ROSING: Yes. As a cardiologist,  14 I would come at this with a little different  15 approach.  16       First of all, I don't think there's  17 any evidence in the short-term study that  18 there was any cardiovascular risk at all.  19 And even though there's a  20 question -- Dr. Hennessy raised the question  21 of arrhythmias, this was a blinded study and  22 there were no arrhythmias. And just as</p>	<p style="text-align: right;">317</p> <p>1 don't have. I brought up the question of  2 other drugs, but I didn't bring the question  3 up a second time because I was convinced that  4 the problem is not the seven or the nine  5 events. The problem is the zero events, that  6 if you take a patient population with these  7 risk factors, including age, which the  8 average age was in the sixties, you'd be very  9 surprised over the course of a year, with an  10 intervention such as surgery and other  11 stresses, that you wouldn't come up with at  12 least one or two or more events.  13       So as a cardiologist, I think I'd  14 be less concerned and be willing to accept  15 the short term use of this drug.  16       DR. BUCHMAN: Dr. Krist?  17       DR. KRIST: I still feel the same way  18 I felt before when I had my little rant. And I  19 disagree some, in the sense that, to me, what's  20 different here is that it's not that it's  21 questionable as to whether there's risks long  22 term and beyond 14 days. I'll take it a step</p>

<p style="text-align: right;">318</p> <p>1 further than what Dr. Kramer said. We need to  2 look at it past 14 days. There's no systematic  3 data collection beyond the short term use of the  4 medicine.  5 And even building on some of what  6 Jay said, I am concerned about, well, what  7 would it take to evaluate this? But if you  8 look at the Study 014, to at least see this  9 blip, it didn't take that many people to see  10 the blip. Now, it's not enough people to  11 reach statistical significance, but it's  12 enough to raise safety concerns, which I  13 think is different than looking at an  14 efficacy outcome.  15 DR. BUCHMAN: Dr. Lincoff?  16 DR. LINCOFF: So I guess our role here  17 is really to focus on the cardiovascular, "our"  18 being the cardiologists. And I'm trying to put  19 that in the context of what I would expect from  20 other therapies and be concerned about.  21 I really do think there is a  22 difference between long- and short-term</p>	<p style="text-align: right;">320</p> <p>1 albeit the longest study, one-third of the  2 patients showing what appeared to be a  3 numeric excess ended up being seven events.  4 Those events, that excess, if it  5 existed -- because it didn't in the  6 adjudicated, although that's with mixing of  7 the MI being mixed with less severe unstable  8 angina, et cetera. So if we just say we're  9 going to talk about MI and we're not going to  10 care about the others, even though they're  11 mechanistically similar so you would have  12 expected them all to trend in the same  13 direction, but if you say we're just going to  14 talk about MI, then what we're talking about  15 is in the first three to four months of this  16 large study, this study with one-third of all  17 the patients in the OBD, you had these excess  18 events.  19 In two-thirds of the patients in  20 the other studies whose follow-up range from  21 one to three months, that same period, that  22 three to four months, you didn't see any</p>
<p style="text-align: right;">319</p> <p>1 therapy. Cumulative effects have impact with  2 some types of therapies, and corticosteroids  3 are obviously an example of that, because the  4 effect on bone may be cumulative.  5 But if we think about mechanisms of  6 ischemic cardiovascular events, it's either  7 progression of atherosclerosis, plaque  8 instability, thrombosis, vasoconstriction.  9 And it's hard to postulate how a short-term  10 therapy would lead to a long-term risk.  11 Now, that only goes so far.  12 Obviously, theory and pathophysiology are  13 important up to a point, but in the end, you  14 have to go by what your empiric data is. And  15 so what we have here is empirically not a  16 hint of any signal in short term, albeit with  17 incomplete follow-up, but for what we have,  18 no imbalance, virtually no events in this  19 short-term follow-up.  20 And in long-term follow-up, in a  21 study that was one-third of the total  22 patients tested for this OBD indication,</p>	<p style="text-align: right;">321</p> <p>1 excess. In fact, there was almost a  2 countervailing less -- numerically less than  3 the active drug arm.  4 So it's not to say it isn't real.  5 The reality is we don't know what we would  6 see if we duplicated this 14. But it's not a  7 strong signal. It's a signal that gives us a  8 lot of question of stability with one or two  9 events in either direction, with one or two  10 extra events in the placebo group that one  11 would have expected based upon the patient  12 population. And so it's a very weak piece of  13 evidence. And it's a piece of evidence that  14 I'd have trouble hanging my hat on even for  15 an approval of a long-term indication.  16 But certainly to then go back and  17 say I've got a very short-term indication for  18 which we have no signal at all and we can't  19 mechanistically calculate -- or we can't  20 mechanistically postulate why there should  21 be, I have a lot of trouble.  22 So the long and short is, for the</p>

322	<p>1 short-term indication that we're talking  2 about, even though the dose is much higher,  3 of course, I don't have a concern for  4 cardiovascular risk.  5 DR. BUCHMAN: Dr. Kramer?  6 DR. KRAMER: I'd like to shift the  7 conversation to something that Dr. Pasricha  8 raised, which is what are we to do about this?  9 I mean, we can talk all afternoon, and part of  10 the reason we're talking so much is because  11 there's a lot of missing information, and you  12 can only go so far with mechanistic discussions.  13 But the question is what are our options?  14 I think there are a couple of  15 options that maybe you didn't list that -- I  16 didn't see in the plans outlined by the  17 sponsor, if this drug were to be approved,  18 any suggestion that there even be a registry  19 of all patients that are taking this drug  20 with follow-up, or that there be any  21 observational studies in large health plan  22 databases or any -- you know, as this drug is</p>	324	<p>1 So I think that often happens in  2 clinical trials, that the placebo event rate  3 is lower than you thought it would be.  4 DR. BUCHMAN: I think that was worth  5 including you.  6 We're going to move on. Oh, was  7 there one other? Dr. Epstein?  8 DR. EPSTEIN: Yes, I just wanted to  9 say that the three things that were asked, the  10 cardiovascular events, I agree there was no  11 signal in the short-term study. And to be able  12 to do a follow-on study, that just statistically  13 based on the numbers, even that you saw in the  14 long-term OBDs, would be very impractical.  15 And I've often heard about these  16 registries and things at various panel  17 meetings, but that's a huge thing to require  18 for something with a very small signal. So I  19 don't necessarily follow along with that.  20 And again, the other thing we were  21 asked is neoplastic. I agree with everyone  22 else that there was a very scattered signal,</p>
323	<p>1 on the market, if we just depend on passive  2 reporting, we're going to be in the same  3 situation we're in right now in the future,  4 which is we will not have any information to  5 add to the database. So I'm disappointed  6 that there isn't some plan to actively  7 solicit cardiovascular safety in the long  8 term, and I'd like to see that laid out, I  9 would suggest.  10 DR. BUCHMAN: Dr. Proschan, did you  11 have a comment?  12 MR. PROSCHAN: I didn't have my hand  13 up, but now that you called on me, I will say  14 something.  15 DR. BUCHMAN: You stuck your light on.  16 MR. PROSCHAN: And that is that I  17 think the argument that there are not enough  18 placebo events, exactly the same argument was  19 made in the cardiac arrhythmia suppression  20 trial. It's not that these drugs are killing  21 people. It's those -- you know, placebo  22 patients aren't dying enough.</p>	325	<p>1 and again, not short term.  2 And the bone fractures, I don't  3 know, was the floor more slippery in  4 those -- no. But that didn't seem to have  5 any real signal. So I don't see anything in  6 the pooled data on the short-term studies  7 that would indicate that there's any  8 particular concern, particularly in regards  9 to the cardiovascular.  10 DR. BUCHMAN: We're going to move on.  11 Dr. Pasricha, last point and then  12 we're going to move on.  13 DR. PASRICHA: No, no, just for the  14 record, I want to clarify. On the bone  15 fractures thing, I think that was the only  16 signal that was actually statistically  17 significant, wasn't it? That is the only one  18 with a 95 percent confidence interval that did  19 not cross -- so actually, I think as far as the  20 long-term data is concerned that is -- if I  21 remember correctly, that is the most robust  22 signal that we had amongst the three. I just</p>

326	<p>1 don't think it translates into a seven-day 2 course of medication.</p> <p>3 But I want to make sure that we 4 have the record straight on that. Is that 5 correct?</p> <p>6 DR. KORVICK: Can you repeat your 7 question?</p> <p>8 DR. PASRICHA: The clarification was 9 whether the fracture risk was statistically 10 significant. If I recall from Dr. Dannis' 11 presentation, it was. I just want to make sure 12 we have that on the record.</p> <p>13 DR. BUCHMAN: I think the lower was 14 .99, which was still -- is my memory correct. 15 that it actually kind of approached 0 as well?</p> <p>16 MS. CASTILLO: This is Sonia Castillo, 17 FDA. For Study 014, it was significant. For 18 the non-cancer and cancer population combined, 19 it was not. Let's see, for the combined cancer 20 and non-cancer population, confidence interval, 21 95 percent, for the relative risk was .6 to 2.3. 22 And for the Study 014, confidence interval was</p>	328	<p>1 12-milligram capsules in the short term, that 2 is seven days or 15 doses, for patients 3 following partial large or small bowel 4 resection surgery with primary anastomosis 5 with regard to the cardiovascular events, 6 neoplastic events, and/or bone fractures? 7 Just the cardiovascular? 8 DR. KORVICK: Please. 9 DR. BUCHMAN: Did you want three 10 separate votes or no? 11 DR. KORVICK: I think we've got a lot 12 of input on the other, but the first one seems 13 to be an issue. 14 DR. BUCHMAN: So just for 15 cardiovascular events. Can I have a show of 16 hands for all those that do have concern with 17 the cardiovascular risk profile? 18 Please keep your hands up and state 19 your name and then you can put it down. 20 Dr. Krist, do you want to start? 21 DR. KRIST: Krist, yes. 22 MR. PROSCHAN: Proschan, yes.</p>
327	<p>1 1.1 to 10.4.</p> <p>2 DR. BUCHMAN: Dr. Hennessy?</p> <p>3 MR. HENNESSY: A very quick comment. 4 I think that the way to address a safety signal 5 is to do a study, even if it's difficult. 6 Saying that we wouldn't require one because it's 7 difficult essentially says that we're dismissing 8 the safety concern. I'm uncomfortable doing 9 that, particularly for a drug that is not 10 life-saving, but is dollar-saving.</p> <p>11 DR. BUCHMAN: We're going to move on 12 to --</p> <p>13 DR. KORVICK: We would be interested 14 if the chair would be willing to ask the members 15 to vote on the first bullet of whether or not 16 they think that there is an issue for the short 17 term use for cardiovascular.</p> <p>18 DR. BUCHMAN: Absolutely. We can do 19 that as an official vote. So let's do that now, 20 and I'm going to read the question. 21 Based on currently available data, 22 do you have concerns for the use of alvimopan</p>	329	<p>1 DR. PASRICHA: Pasricha, yes. 2 DR. RICHARDSON: Richardson, yes. 3 DR. CHANG: Chang, yes. 4 DR. KRAMER: Kramer, yes. 5 DR. BUCHMAN: Buchman, yes. 6 MR. HENNESSY: Hennessy, yes. 7 DR. BUCHMAN: All those that vote no? 8 Keep your hand up until you say your name and 9 your vote's recorded. 10 We'll start over here, 11 Dr. Talamini. 12 DR. TALAMINI: Talamini, no. 13 DR. EPSTEIN: Epstein, no. 14 DR. LINCOFF: Lincoff, no. 15 DR. LEVINE: Levine, no. 16 DR. CULLEN: Cullen, no. 17 DR. ROSING: Rosing, no. 18 DR. BUCHMAN: Any abstentions? 19 MS. CORKERY-DeLUCA: DeLuca, 20 abstained. 21 DR. BUCHMAN: The state of Florida is 22 calculating the vote.</p>

330	<p>1 MS. PHAN: We have eight yes, six no, 2 and one abstain.</p> <p>3 DR. BUCHMAN: We're going to move on 4 to Question No. 4, which is a voting question. 5 Do we want to take a break? We 6 need a potty break, I guess.</p> <p>7 Okay, let's take a break. I forgot 8 about that. I was so excited about how we 9 were moving along here. So let's take a 10 15-minute break -- actually 13 minutes. If 11 everybody could be back here at 3:15 sharp, 12 we'll move on to Question No. 4.</p> <p>13 (Recess)</p> <p>14 DR. BUCHMAN: If I could have 15 everybody's attention, please. There is one 16 comment that I want to clarify for the press. 17 First off, I am going to give a 18 brief chair summary of each of the questions 19 at the end of today. But for those from the 20 press that want to scram and not wait to see 21 if I have a surprise up my sleeve, in regard 22 to the vote that we had on Question No. 3, it</p>	332	<p>1 and look to the economic argument because it's 2 easily quantified. But as a surgeon, I would 3 also say that lying in a hospital bed for 12 or 4 24 additional hours with a bloated belly and not 5 eating is not a healthy condition. It's much 6 harder to quantify what is not healthy about 7 that and measure it.</p> <p>8 But I think most of us who take 9 care of patients on a daily basis know 10 empirically that that is not a healthy thing, 11 and that if you reduce that by some 12 percentage, you're improving the patient's 13 overall care. So I just wanted to get away 14 from this idea that the only thing sitting on 15 the benefit side is economic. I don't 16 believe that that's true.</p> <p>17 DR. BUCHMAN: Dr. Epstein? 18 DR. EPSTEIN: As a treating clinician 19 who deals with a lot of patients with ileus, it 20 is a very unpleasant condition. And if you can 21 shorten that, I think, for the patient's 22 benefit, you've really made a great improvement</p>
331	<p>1 was not originally designed to be a voting 2 question. We changed that. But what we 3 voted on, as a committee, was only whether we 4 had concern about the cardiovascular risk 5 effects. We did not vote on whether we had 6 concern about neoplastic events or bone 7 fractures, although obviously those were 8 discussed.</p> <p>9 We're going to move on to Question 10 No. 4, which is a voting question. Do you 11 believe the overall benefits of treatment 12 with alvimopan outweigh the potential risks 13 for short-term in-hospital use in patients 14 with partial large or small bowel resections 15 with primary anastomosis?</p> <p>16 I'm going to start, actually, on 17 this side with Dr. Talamini, what comments 18 you have.</p> <p>19 DR. TALAMINI: I want to just speak 20 for a moment to the potential benefits of a 21 strategy like this. Certainly the economic 22 argument is there, and it's easiest to fall into</p>	333	<p>1 in their overall outcome of health. And whether 2 it's 12 hours or 24 hours, that's very 3 significant.</p> <p>4 DR. BUCHMAN: Dr. Lincoff? 5 DR. LINCOFF: I agree with that, and I 6 want to emphasize that -- although we brought up 7 the financial issues, I don't think that that's 8 the key here at all. I mean, what we do in 9 medicine is to make people live longer or to 10 prevent unpleasant things in terms of make them 11 feel better, and this is the latter, and I think 12 it's very real.</p> <p>13 DR. BUCHMAN: Dr. Hennessy? 14 MR. HENNESSY: While I'll agree that 15 there is a clinical benefit to the patient 16 rather than just to the hospital, and I'll admit 17 that I don't see patients, it seems to me from 18 looking at the numbers that the benefit can be 19 characterized as modest or even marginal. And 20 this is a drug that clearly doesn't save lives, 21 and for which there's a significant signal of a 22 cardiovascular risk from a randomized trial.</p>

<p style="text-align: right;">334</p> <p>1 And in my mind, the benefit does not outweigh 2 the risk while that concern has not been 3 addressed. 4 DR. BUCHMAN: I would echo 5 Dr. Hennessy's comments in that we're looking at 6 a benign condition. And clearly, I think the 7 drug, as we discussed earlier in this session, 8 does have some efficacy and has physiologic 9 effect. It's not very great, but it is 10 statistically and perhaps marginally clinically 11 significant. 12 We're asked to make a risk-benefit 13 analysis here. We're dealing with a benign 14 condition with fairly marginal but clinically 15 significant effects of a drug. So therefore, 16 it really can't tolerate any potential for 17 significant side effects. And my concern is 18 that the denominator, that is the risk 19 potential, not necessarily the risk, but the 20 risk potential, does at a minimum slightly 21 outweigh the potential benefit for the 22 patients.</p>	<p style="text-align: right;">336</p> <p>1 It's not really about that much more. But so I 2 obviously think that's very important. 3 I think this is tough because I do 4 have concerns, but I feel that the signal 5 really is more in the long-term data, and 6 it's a different patient population. So I 7 would feel more comfortable if there was some 8 monitoring of the patients that did get the 9 drug. I feel very uncomfortable just giving 10 it to anybody. 11 Just because you brought this up a 12 couple times, Judith, is that there is a 13 study on alvimopan in chronic constipation 14 with no opioids and it didn't show efficacy, 15 so I don't know how well it will help. And 16 this is a different patient population, even 17 if you didn't give opioids after a surgery, 18 but I'm not sure how efficacious the drug 19 would be if you're not on an opioid. 20 DR. BUCHMAN: Dr. Richardson? 21 DR. RICHARDSON: I guess I'm troubled, 22 as everyone else seems to be. Clearly, there</p>
<p style="text-align: right;">335</p> <p>1 Dr. Kramer? 2 DR. KRAMER: I would love to see a 3 study that compared the effects of this drug in 4 PCA-controlled analgesia after a bowel resection 5 to an alternative pathway that was a postop 6 pathway that involved opioid-sparing techniques, 7 such as what occurred in the European study. I 8 don't think we've demonstrated that this should 9 be -- have a blanket indication for bowel 10 resection surgery; I think it should -- as I've 11 said many times before, bowel resection surgery 12 in the setting of PCA. And I echo the comments 13 of Dr. Buchman and Hennessy. I would not say 14 yes to this question based on my concerns about 15 risk, and the fact that it has been studied only 16 in the setting of PCA. 17 DR. BUCHMAN: Dr. Chang? 18 DR. CHANG: I think this is a really 19 tough question, but when I brought the cost 20 effective, that was just one example of 21 measuring clinical meaningfulness. I mean, I 22 take care of -- it's all about how they feel.</p>	<p style="text-align: right;">337</p> <p>1 are some benefits to the various parties that 2 are involved in this. The sponsor, obviously. 3 The hospitals I think certainly can benefit from 4 this. I think if you look at the patients, 5 though, I think that benefit is much more 6 difficult to describe. 7 I was quite taken by the effects of 8 this with respect to use of PCA or not. I'm 9 particularly interested in the effects of 10 ketorolac in this group. Unfortunately, I 11 don't see anybody who is a generic maker of 12 ketorolac out there promoting that drug for 13 this indication, so that I don't think we'll 14 ever see that type of study find the light of 15 day. 16 I'm also troubled by the fact that 17 the number needed to treat -- if you combine 18 the GI-2 and GI-3, which I think 19 realistically, one probably should do because 20 I don't see that there's a great deal of 21 difference in those criteria, it seems to me 22 that the number needed to treat is probably</p>

<p style="text-align: right;">338</p> <p>1 around 10 patients to see one patient  2 benefit. In medical oncology, at least, a  3 10 percent response rate would be regarded as  4 a failure. And I don't see that the overall  5 benefits are adequate for the patients.  6 I'm also troubled by the fact that  7 the RiskMAP doesn't include any sort of input  8 from the patients in this, but we'll wait  9 until we get to that.  10 DR. BUCHMAN: Ms. Corkery-DeLuca?  11 MS. CORKERY-DELUCA: JoEllen DeLuca.  12 As a patient that's had a lot of bowel surgery,  13 I'll tell you, every day out of the hospital is  14 a good day. And I protest mightily when I have  15 to go in. And if I'm your patient and you're  16 going to be doing an NG tube, you're going to be  17 in for the fight of your life.  18 I didn't feel that the  19 cardiovascular events -- to me, the GSK  20 seemed to be more of a risk than the Entereg.  21 The bone fractures, when you start picking up  22 with age, when we start looking at people</p>	<p style="text-align: right;">340</p> <p>1 me say maybe this is a time when we should  2 make a stride with a drug that is looking  3 small and then -- even if we have to revisit  4 it later. I mean, there is not anything else  5 like this.  6 And I'm not just looking from my  7 hospital's bottom line. They don't need  8 another 12 hours. And I've been in the  9 hospital for a weekend because the surgeon  10 didn't make it. He had too many things to do  11 and didn't make it on Friday before closing  12 time and the nurses were gone, so I had to  13 stay until Monday. So I think we can argue  14 the 12 hours or the 24 hours, but the reality  15 is, it's who -- which of the nurses got the  16 paperwork ready or not. So I think the 12  17 hours or the 24 is sufficient for most  18 general purposes. And my hospital is fairly  19 large, so it's not a matter of just being a  20 little community hospital.  21 So that's how I would feel. I  22 think that the risk for a patient, that a lot</p>
<p style="text-align: right;">339</p> <p>1 being age 65 and up, that to me was what made  2 me say I think I should abstain.  3 Because I am a patient, I don't  4 know enough, but bone fractures are something  5 that -- you're lying down, you're hitting 65,  6 you're hitting 70, you're hitting 75, and I  7 think that you're going to be much more  8 likely to stand up and fall and injure  9 yourself that way than perhaps even a  10 cardiovascular event.  11 The overall benefits, even reading  12 between the lines I think that some of the  13 questions have been answered. And looking  14 back towards an answer, at least in my mind,  15 looking back toward how hospitals will handle  16 this, I'm still not sure when gut surgery  17 moves from doing one large bowel resection to  18 another for another comorbidity factor,  19 whether we're -- who's going to handle that.  20 But as a patient, I think sometimes  21 we have to make strides when we can make  22 strides. And the overall risk, to me, made</p>	<p style="text-align: right;">341</p> <p>1 of us that have been in the hospital a lot  2 for bowel resections, would say it's worth  3 it.  4 DR. BUCHMAN: Dr. Levine?  5 DR. LEVINE: I'm more on the fence  6 than ever, but I would say that, no question  7 about it, as Dr. Hennessy and others point out,  8 the hard data is marginal, modest, whatever you  9 want to call it. It's not very, very  10 significant. Again, I'm unimpressed, or  11 relatively unimpressed, that there's a dose  12 response data shown that's very significant  13 between 6 milligrams and 12 milligrams.  14 On the other hand, there's no  15 question, not only for the patient, but for  16 the physician and everyone else, it is a big  17 difference in seeing patients like this, if  18 they can get that tube out in 12 hours or 24  19 hours. And the patients feel better, it's  20 important, and I think we're going to have to  21 have very strict risk management control  22 here, but I definitely feel that probably the</p>

<p style="text-align: right;">342</p> <p>1 patient outweighs it here than just the  2 cost-effectiveness. And I think for the  3 patient's sake, I would probably agree that  4 the benefits marginally overcome the  5 negatives.  6 DR. BUCHMAN: Dr. Pasricha?  7 DR. PASRICHA: I'd like to start by  8 reinforcing the concept that while the  9 discussion may have been a little heavy on the  10 health care costs of this drug, I don't think  11 that's what's driving the decision. I want to  12 make sure that at least that's on the record.  13 Dr. Buchman, you mentioned that  14 this is not a life-threatening condition, and  15 that is true. But as somebody who's made a  16 career of looking after patients who have  17 chronic nausea, I can tell you next to dying,  18 nausea is probably the most bothersome  19 symptom that patients have. And if you can  20 make a difference in that, it's a big  21 advance.  22 So I would just like to say that,</p>	<p style="text-align: right;">344</p> <p>1 POI -- is that similar? And the answer to  2 that is I just don't know. And that's what  3 bothers me is maybe that's right. Maybe you  4 have to be on this drug long term to feel any  5 harm, to have any problems. But I just don't  6 know that and I don't have strong evidence  7 that that's the case. I have some suggestion  8 that that's the case, but I don't have strong  9 evidence.  10 So for me, the benefit of reducing  11 by one day versus the potential for an MI or  12 something else is enough.  13 Maybe I'm just a 'fraidy cat, but  14 that's enough to make me think, no, I  15 wouldn't. I think the risks outweigh the  16 benefit.  17 DR. BUCHMAN: Dr. Krist?  18 DR. KRIST: I'll echo what some of the  19 others have said. And the way I think about it  20 with this question, we're asked to do a  21 benefit-to-risk analysis. And I think, if you  22 look on one level, quality of life-type</p>
<p style="text-align: right;">343</p> <p>1 and in that context, I actually was a little  2 struck that the sponsor has not gone beyond  3 some very simple measures and not, for  4 instance, included any surrogate measures of  5 quality of life or global sense of helping in  6 their outcome. And I just -- maybe this is  7 the time to ask them whether they have any  8 data that actually looks beyond the objective  9 points, such as we saw with GI-2. But also  10 got a global sense from the patients if they  11 had any questions that might actually  12 reinforce what we're saying here.  13 DR. BUCHMAN: Dr. Proschan?  14 MR. PROSCHAN: I agree with the  15 comments that this is -- as far as the potential  16 harm, I mean, this is no slam dunk. I am  17 persuaded that the signal is real for OBD. Even  18 that's not a slam dunk, but I am persuaded that  19 that's real. I don't see a reason to throw out  20 014. And so I'm more persuaded than not that  21 that's real.  22 Now, the question then becomes is</p>	<p style="text-align: right;">345</p> <p>1 measures, clearly having a postoperative ileus,  2 having increased nausea and vomiting, having an  3 NG tube, are significant things.  4 And I think we've seen relatively  5 clear data suggesting that this medication  6 reduces those risks.  7 And we do see decreased nausea and  8 vomiting, in a sense, when you look at the  9 adverse events. And people are more likely  10 to stop placebo than the intervention drug  11 because of nausea and vomiting. And then if  12 you look at quality of life risks, like how  13 people feel and those types of side effects,  14 this medicine seems beneficial.  15 Where I get lost is looking at  16 major morbidity and mortality. And as  17 Dr. Hennessy has pointed out, in the studies,  18 we don't see reduction in mortality from the  19 medication. We don't see reduction of  20 thromboembolic disease or nosocomial  21 infection, and those significant things. It  22 could happen from a reduced hospital stay,</p>

346	<p>1 and that's where I think there's benefit.  2 But we don't see that in our studies. We  3 don't even see a signal of that. And to me,  4 the significant morbidity/mortality risks is  5 a black box and we can't answer that. And  6 because it's a black box, that makes me more  7 afraid overall about the benefit-to-risk  8 ratio.</p> <p>9 DR. BUCHMAN: Dr. Cullen?  10 DR. CULLEN: As a surgeon, what a  11 patient complains about, there's really  12 basically three things postoperatively they  13 complain about: pain, which you can take care  14 with a PCA or something else; an NG tube, if  15 they have one, which is a miserable experience,  16 and their study shows that it reduces the  17 incidence of reinsertion; and then the  18 distention, they're not feeling very good  19 because they're distended, nausea, and vomiting.  20 And the study demonstrates that it's efficacious  21 in that respect. So I think the benefits of the  22 medication are there.</p>	348	<p>1 DR. BUCHMAN: So it looks like the  2 surgeons and gastroenterologists are going to  3 have to duke it out in the parking garage after  4 the meeting.</p> <p>5 Dr. Rosing, as a cardiologist, what  6 are your feelings in terms of the  7 risk-benefit analysis here?  8 DR. ROSING: I think the  9 gastroenterologists are also going to have to  10 battle the cardiologists, along with the  11 surgeons. I've heard from the patient advocate,  12 I've heard from some of the gastroenterologists,  13 and certainly both of the surgeons. I've read  14 the data and I think there is some benefit that  15 arrives from this drug beyond the economic  16 benefits. And I really don't see any risk from  17 the short-term studies at all. I do respect  18 some of my colleagues' concerns, though, and I  19 think it would be reasonable to ask the sponsor  20 to implement some form of long-term monitoring  21 for this drug.  22 DR. BUCHMAN: I would just add one</p>
347	<p>1 The stress of surgery is -- it's  2 not like running a marathon, but it is a  3 stressful situation on the cardiovascular  4 system and the pulmonary system. So you're  5 adding a medication to this already stressful  6 system and you're not seeing an increased  7 risk of cardiac events. So in the short  8 term, I understand everybody's concerns, but  9 I don't see the increased risk.</p> <p>10 And then finally, my concern with  11 this drug is if it was approved in a  12 hospital, that my orthopedic surgery  13 colleagues would use it and my vascular  14 surgery colleagues would use it, and anybody  15 who had anything done would use it, where it  16 wasn't -- the studies didn't show an efficacy  17 in those type of operations. And that's a  18 concern I have in the back of my mind.</p> <p>19 But those other two things I  20 mentioned, unless you've been a patient  21 sitting in a hospital with an NG tube, you  22 don't know how miserable that is.</p>	349	<p>1 last comment before we come to a vote. There  2 was an interesting paper a couple of years ago  3 that looked at all the drugs ever approved by  4 the FDA. And as I recall, not the difference  5 between the effect of placebo and study drug,  6 but the benefit over placebo was actually only  7 20 percent. But if we look at NG tube  8 reinsertion in this study, the difference  9 was -- sure, the difference was 43 percent, but  10 the real difference was 11 percent versus  11 6 percent.</p> <p>12 Let's put it in perspective. We're  13 looking at small numbers in terms of risk.  14 We're looking at small numbers in terms of  15 benefit.</p> <p>16 So with that, I'm going to ask are  17 there any other comments from the committee,  18 any rebuttals or re-rebuttals?  19 Dr. Epstein?  20 DR. EPSTEIN: Just one comment. I'd  21 like to point out we've heard about ketorolac as  22 a opioid-sparing drug. And as a</p>

350	352
<p>1 gastroenterologist, if you want to talk about  2 risk, start putting a lot of people on ketorolac  3 and you'll see a lot of risk.  4 DR. BUCHMAN: Don't tell people that.  5 That's how we make money.  6 DR. EPSTEIN: And the other thing is,  7 just in terms of cardiac -- we've heard from  8 Duke, we've heard the adjudicated data, we've  9 heard from our cardiologists, we've seen no  10 signal in any of the combined short-term  11 studies. We're dealing with the fact that the  12 placebo happened to have a zero number, and so  13 we're dealing with a little bit of the tyranny  14 of small numbers here. And I think it's a leap  15 of faith to think that there's a big cardiac  16 risk in the short term. That's just my opinion,  17 based on the global cumulative data that we've  18 heard today.  19 DR. BUCHMAN: I'm going to go ahead  20 and read the question and then we're going to go  21 for our vote.  22 The question again from the agency</p>	<p>1 MR. HENNESSY: Hennessy, no.  2 DR. BUCHMAN: Buchman, no.  3 DR. KRAMER: Kramer, no.  4 DR. RICHARDSON: Richardson, no.  5 MR. PROSCHAN: Proschan, no.  6 DR. KRIST: Krist, no.  7 MS. PHAN: We have nine yes and six  8 no, no abstain.  9 DR. BUCHMAN: We're going to move on  10 to Question No. 5, which is also a voting  11 question. If alvimopan is approved for the POI  12 indication, do you believe Adolor Corporation's  13 proposed risk management plan is adequate to  14 address the potential risks?  15 Explain what features of the  16 proposal would be most desirable.  17 Dr. Rosing, let's start with you.  18 DR. ROSING: I think we can refocus on  19 the questions that have been raised about the  20 long-term effects, even though it's short term  21 use of this drug. And I think that the features  22 of the proposal that are not adequate would be</p>
351	353
<p>1 is, do you believe the overall benefits of  2 treatment with alvimopan outweigh the  3 potential risks for short-term in-hospital  4 use in patients following small or large  5 bowel resections with primary anastomosis?  6 All of those that feel that the  7 benefit outweighs the risk, please raise your  8 hand, and keep them up until you state your  9 name.  10 Let's start over here with  11 Dr. Rosing.  12 DR. ROSING: Rosing, yes.  13 DR. CULLEN: Cullen, yes.  14 DR. PASRICHA: Pasricha, yes.  15 DR. LEVINE: Levine, yes.  16 MS. CORKERY-DELUCA: DeLuca, yes.  17 DR. CHANG: Chang, yes.  18 DR. LINCOFF: Lincoff, yes.  19 DR. EPSTEIN: Epstein, yes.  20 DR. TALAMINI: Talamini, yes.  21 DR. BUCHMAN: All those that vote no,  22 state your name.</p>	<p>1 that I think there should be some form of  2 long-term monitoring for the three signals that  3 were identified in Study 014, namely  4 cardiovascular complications, fractures, and  5 neoplasia.  6 DR. BUCHMAN: Dr. Cullen?  7 DR. CULLEN: I agree with Dr. Rosing.  8 I think specifically the cardiovascular effect  9 should be monitored long term.  10 DR. BUCHMAN: And Dr. Proschan? All  11 right, Dr. Krist, I'm sorry I forgot you.  12 DR. KRIST: I don't think that the  13 risk management plan is adequate. We have a big  14 black box on long-term safety, and the plan  15 doesn't do anything to address that.  16 DR. BUCHMAN: Dr. Proschan?  17 MR. PROSCHAN: I don't have a good  18 sense of whether it would be adequate or not, so  19 I really don't know.  20 DR. BUCHMAN: Dr. Pasricha?  21 DR. PASRICHA: I'd like to see a  22 surveillance program for cardiovascular risk.</p>

354	<p>1 And secondly, I'd like to make sure that as far 2 as possible, we've put restriction on off-label 3 use for now. And that means perhaps more 4 narrowly define the target population that this 5 is really indicated.</p> <p>6 DR. BUCHMAN: Dr. Levine?</p> <p>7 DR. LEVINE: I definitely agree with 8 the latter point. I also feel that there should 9 be a much stricter approach in our past meetings 10 with an already approved drug disparity. We 11 noted that we used the touch phone. I think 12 something in that line is really necessary for 13 follow-up here. I think we have to be -- it 14 would answer the question for short term and 15 otherwise if we had a very strong type of risk 16 management program, which we didn't hear from 17 yet -- about from the sponsor.</p> <p>18 DR. BUCHMAN: Ms. Corkery-DeLuca?</p> <p>19 MS. CORKERY-DELUCA: I'm JoEllen 20 DeLuca. For the long-term risk, I would like to 21 see something more done about that. I think we 22 owe it to the people who look for what the FDA</p>	356	<p>1 walk up to them when 10 other people are asking 2 them to initial the site of their operation in 3 the preop area and -- oh, by the way, we want to 4 give you this drug. We're a little uncertain 5 about the cardiac risks on this, but trust us 6 and everything will be all right -- I don't 7 think that's an adequate way of addressing that. 8 I think patients have to have more information 9 and some input into this decision.</p> <p>10 DR. BUCHMAN: Dr. Chang?</p> <p>11 DR. CHANG: There's parts of this that 12 I like, that it is restricted to bowel resection 13 and they're making sure it's only for hospitals. 14 I think that they've put some things in here 15 that are very good. I guess I'll have to think 16 about the emergency surgeries. Sometimes you 17 can't always give the patient all that 18 information or they really don't care. But I do 19 think that not only just looking at long-term 20 monitoring, I think they should look at some 21 predictors if someone comes in, like baseline 22 characteristics of age or gender or</p>
355	<p>1 approves and not approves to say that there are 2 risk factors. And for me, particularly, the 3 cardio and the osteo.</p> <p>4 And I didn't know, how can we 5 monitor this? I don't know that. But that 6 is a question for me. And the off-label use, 7 it goes back again to my question about 8 letting the horse out of the barn. If it 9 goes then to bariatric or if it goes to then 10 to another use entirely that we're not 11 discussing today, who does that? Who is 12 going to monitor that? I don't know.</p> <p>13 DR. BUCHMAN: Dr. Richardson?</p> <p>14 DR. RICHARDSON: I think we need to 15 provide patients with a little more information 16 on this. The RiskMAP talked about getting some 17 sort of verbal consent from patients as they're 18 being wheeled into the OR, and I don't think 19 that's adequate. I think people have to have 20 some written information that they can digest, 21 say 24 hours before their procedure. I think 22 the idea of having some health care provider</p>	357	<p>1 cardiovascular risk factors, and cancer or not 2 cancer.</p> <p>3 I think there are some things that 4 may -- information they can get to figure out 5 who may have the greater benefit over risk 6 than others.</p> <p>7 DR. BUCHMAN: Dr. Kramer?</p> <p>8 DR. KRAMER: I think the proposed risk 9 management program is predicated on process 10 measures of assuring that it only be used in the 11 inpatient setting and not outpatient. I agree 12 with the comments that have been made that I 13 think we need to go beyond that and look at 14 clinical endpoints. As I've said many times, I 15 believe the indication should be specified that 16 it be given in the context of opioid PCA.</p> <p>17 And I agree with the comments about 18 trying to more carefully prevent off-label 19 use. I'm concerned that once this is 20 available, that anybody doing surgery where 21 they think there's a chance of ileus might 22 prescribe it, and therefore, increasing the</p>

<p style="text-align: right;">358</p> <p>1 population potentially at risk.  2 I agree with the idea of trying to  3 get consent. I realize this is challenging,  4 but I think that patients should be informed.  5 And I was concerned -- I heard a presentation  6 recently within the last year by a wholesaler  7 about what the impact of all these various  8 risk management programs is having on their  9 ability to function. They're an industry,  10 I've learned from this presentation, that  11 operates in a very slim margin of ability to  12 manage, and really, the main brunt of this  13 program is put on the wholesalers. So I  14 agree with the FDA's comments that it really  15 shouldn't be the wholesaler trying to sort  16 out who gets this drug, and that the sponsor  17 should take on some of that cost and  18 responsibility.  19 DR. BUCHMAN: Quite frankly, I think  20 that the RiskMAP proposed by the company was  21 done haphazardly, and it looks like very little  22 time was really put into it. It's very, very</p>	<p style="text-align: right;">360</p> <p>1 together than we can as physicians, and I'm  2 just disappointed in what I saw.  3 MR. HENNESSY: Sean Hennessy. I think  4 that this drug needs additional study to  5 characterize its cardiovascular risks. I'm not  6 convinced that it needs a risk management action  7 plan. Reading from Dr. Weaver's Slide 8, when  8 should a RiskMAP be considered? When the risks  9 are serious and preventable. When safe and  10 effective use calls for specialized health care  11 skills or settings. When a RiskMAP encourages  12 appropriate use increase benefits relative to  13 risks. Products in a class of product with  14 similar risks that require a RiskMAP. I don't  15 think any of those criteria apply to this drug.  16 The drug is going to be used in  17 lots of patients, more so than can probably  18 be accommodated by the more stringent risk  19 management action plans that we've seen, like  20 clozapine and patient registries to prevent  21 pregnancies. So in my view, the risks need  22 to be characterized in the context of one of</p>
<p style="text-align: right;">359</p> <p>1 short on specifics. Now, that can all easily be  2 corrected, but I am quite surprised that we've  3 come to the point of having a meeting here.  4 You've had this drug under development for seven  5 years. You've known about these risks, at least  6 since last November, that you didn't come up  7 with a more specific plan other than, well,  8 wholesalers will going to control this. The  9 Pittsburgh Pirates are not going to finish in  10 last place next year because they're going to  11 play better. You really need to have more  12 specifics. You need to define things. "Acute  13 care hospital" was mentioned only once.  14 Otherwise, it's always "hospital." Hospital has  15 various definitions, even including veterinary  16 hospitals.  17 So I think you need to supply  18 definitions. You need to have an algorithm,  19 a framework of exactly how this is going to  20 work, what are your check and balance  21 systems? I mean, really, I mean, you guys  22 can do a better job at this, putting this</p>	<p style="text-align: right;">361</p> <p>1 more epidemiologic studies, but they aren't  2 typically part of risk management action  3 plans. And I don't think that a risk  4 management action plan will be effective for  5 reducing the risks unless there are  6 particular patient populations who can be  7 identified who have better or worse  8 risk-benefit balances. And in the absence of  9 a benefit of the RiskMAP, then it's just  10 added cost and added inconvenience.  11 DR. BUCHMAN: I just want to clarify  12 my response. The RiskMAP here primarily, as I  13 see it, is towards prevention of off-label use,  14 because the concern here was in the long-term  15 patients, again, the chronic opiate users. And  16 there needs to be a clear way in  17 which -- because it's very difficult to regulate  18 off-label use for anything. And this is going  19 to have to be a better attempt to keep it out of  20 the hands of the narcotic addicts, those on  21 methadone, patients in nursing homes, and all  22 these sorts of thing. So I just wanted to</p>

362	<p>1 clarify my remark.</p> <p>2 Dr. Lincoff?</p> <p>3 DR. LINCOFF: I think we need to be</p> <p>4 realistic about the prospects of useful data</p> <p>5 from follow-up long-term epidemiologic studies.</p> <p>6 Such studies are notoriously limited in their</p> <p>7 ability to look at treatment effects, and we've</p> <p>8 got to be realistic. If we force a</p> <p>9 10,000-patient registry of the next 10,000</p> <p>10 patients on-label to get this drug, and we see</p> <p>11 and event rate, we're going to have an event</p> <p>12 rate. And we're going to have no idea if that</p> <p>13 event rate is higher than it would be if</p> <p>14 patients didn't get the drug.</p> <p>15 And we're not going to be able to</p> <p>16 look at risk factors for treatment effect.</p> <p>17 We're going to be able to look at risk</p> <p>18 factors for cardiovascular events, but we've</p> <p>19 got better registries in existence right now</p> <p>20 to do that. So if there's really that much</p> <p>21 concern about what the long-term</p> <p>22 cardiovascular events are as a consequence of</p>	364	<p>1 important up to a point, but realize, we use</p> <p>2 a lot of drugs without much in the way of</p> <p>3 consent that carry much more in the way of</p> <p>4 danger -- drugs for atrial fibrillation and</p> <p>5 some antibiotics, et cetera.</p> <p>6 Hospitals institute programs with</p> <p>7 their pharmacies to require approval of</p> <p>8 specialists, et cetera, before it's given.</p> <p>9 But in reality, there are a lot of drugs that</p> <p>10 have much more evidence of danger that we use</p> <p>11 without elaborate methods of consent, et</p> <p>12 cetera. So I think the main issue should be</p> <p>13 to try to assure that these drugs are used</p> <p>14 within the label.</p> <p>15 DR. BUCHMAN: Dr. Epstein?</p> <p>16 DR. EPSTEIN: I basically second what</p> <p>17 Dr. Lincoff said. We have a very large number</p> <p>18 of trial patients in the pooled data set from</p> <p>19 the short term, and there was no increased</p> <p>20 cardiovascular signal, and that is the intended</p> <p>21 use. I think that the RiskMAP should include an</p> <p>22 order that states -- basically from the</p>
363	<p>1 giving these drugs, then the drug shouldn't</p> <p>2 be approved.</p> <p>3 I personally don't believe that.</p> <p>4 But I also don't believe that the resources</p> <p>5 should be diverted toward elaborate</p> <p>6 registries and epidemiologic studies that</p> <p>7 aren't going to test causation. You can't</p> <p>8 test causation with observational studies,</p> <p>9 and that's really what we want to know. So I</p> <p>10 think efforts should be directed instead</p> <p>11 toward, as several people have said, trying</p> <p>12 to make this drug used only as the label does</p> <p>13 describe.</p> <p>14 And I, too, am a physician, not a</p> <p>15 pharmacist or a manufacturer who can best</p> <p>16 design those systems, but I suspect they</p> <p>17 probably can be designed, especially since we</p> <p>18 are trying to make a wall between outpatient</p> <p>19 and inpatient, which seems to me to be a</p> <p>20 relatively discrete setting that's easier</p> <p>21 than some of the more difficult drugs.</p> <p>22 As for consent, I think consent is</p>	365	<p>1 physician that states simply, for use in a</p> <p>2 patient undergoing bowel resection, to limit it.</p> <p>3 I think the biggest concern would</p> <p>4 be, as mentioned by Dr. Cullen, that the</p> <p>5 orthopedist or some other surgeons might want</p> <p>6 to use the drug off-label. So I think that's</p> <p>7 where we should focus the RiskMAP</p> <p>8 specifically.</p> <p>9 DR. BUCHMAN: Dr. Talamini?</p> <p>10 DR. TALAMINI: I would make a couple</p> <p>11 of points. I would say the risk management plan</p> <p>12 is not adequate because it's currently just an</p> <p>13 outline. And I would encourage the FDA to</p> <p>14 predicate approval on that being filled out to</p> <p>15 their satisfaction.</p> <p>16 Having said that, I think the</p> <p>17 consent issue would be extremely difficult,</p> <p>18 for the same reasons that Dr. Lincoff already</p> <p>19 outlined. I've got a hunch that the</p> <p>20 preoperative antibiotics that we give are</p> <p>21 probably more dangerous than this drug, and</p> <p>22 we just don't have the means to ask consent</p>

366	<p>1 for every single drug that we give during 2 surgery.</p> <p>3 I also know that the story of 4 post-approval studies is not an encouraging 5 one. So my suggestion would be to be very 6 focused there. And from a point of 7 ignorance, I might suggest looking into the 8 NSQIP database, which is becoming ever bigger 9 and more robust, as a potential means to try 10 to answer this question post-approval, if 11 it's approved.</p> <p>12 DR. BUCHMAN: Dr. Kramer, you wanted 13 to clarify your comment?</p> <p>14 DR. KRAMER: Dr. Hennessy's comments 15 made me realize I did want to clarify what I was 16 at least suggesting. I'm personally seeing the 17 RiskMAP as a method of limiting the use until we 18 have more information. And I would actually 19 agree that post-approval epidemiologic studies, 20 while not addressing causation, can identify 21 safety signals. And I think that in an era 22 where we're starting to put together distributed</p>	368	<p>1 for follow-up for a short term use drug. I can 2 see just methodologically that people are going 3 to have low incentive to respond to having used 4 the drug for five days. So I mean, it depends 5 on the methodology used, if you use an existing 6 database or something. But that's some of the 7 fear that I have with some post-surveillance 8 trying to figure this out -- or post-approval 9 trying to figure it out.</p> <p>10 DR. BUCHMAN: Dr. Korvick, with your 11 permission, I'm going to split this into two 12 different votes, with two different questions. 13 The first question being, is a RiskMAP 14 necessary? And the second question being, 15 whether the RiskMAP proposed by the Adolor 16 Corporation is adequate.</p> <p>17 Is the agency in agreement with 18 that, or would you just like the single vote 19 as originally planned?</p> <p>20 MR. PROSCHAN: Didn't we already vote? 21 DR. BUCHMAN: No, that was in another 22 life.</p>
367	<p>1 safety networks, in the order of being able to 2 accumulate 50 million patient lives to look at 3 things, we have several pilot programs going on 4 right now across multiple collaborative centers 5 in this country, and I think we can get 6 information with a control group to try to 7 understand some of these safety signals. And I 8 don't think we should be ostriches just because 9 it's challenging. If there's any concern, we 10 should look. And if it's no concern, then it's 11 a waste of money, but --</p> <p>12 DR. BUCHMAN: Okay, Dr. Korvick? 13 DR. KRIST: I just wanted to -- 14 DR. BUCHMAN: Dr. Krist? 15 DR. KRIST: I just wanted to quickly 16 clarify my answer, too. That's the drawback of 17 going very early on in this. I mean, I agree 18 with both of these comments. I don't think a 19 RiskMAP is going to address this and we need 20 more research. I do worry -- and I wasn't going 21 to say anything until you started talking, 22 Dr. Kramer, I mean, I do worry about response</p>	369	<p>1 DR. KORVICK: I think we'd prefer to 2 go with the way that it's written.</p> <p>3 DR. BUCHMAN: You heard the commander 4 in chief. We're going to go with one single 5 vote. And so that means that you're voting at 6 the same time as to, A, if you think a risk 7 management plan is necessary; and also whether 8 you think the risk management plan as proposed 9 is adequate.</p> <p>10 So all those in favor that the risk 11 management plan is necessary, and as proposed 12 is adequate, please raise your hand.</p> <p>13 DR. EPSTEIN: Point of order. 14 DR. BUCHMAN: Okay, go ahead. 15 DR. EPSTEIN: I'm sorry, Mr. Chairman, 16 can you read the question as written? Because 17 I'm confused about "is necessary" or "adequate." 18 DR. BUCHMAN: I'm going to reread the 19 question then and just going to delete the last 20 sentence. So if alvimopan is approved for the 21 POI indication, do you believe Adolor 22 Corporation's proposed risk management plan is</p>

<p style="text-align: right;">370</p> <p>1 adequate to address the potential risk?  2       So we're not voting on whether you  3 think they need to have a plan, you're voting  4 on whether you think the plan that they have  5 proposed is adequate, just so that everybody  6 understands that. Okay?  7       DR. KORVICK: That's correct.  8       DR. BUCHMAN: So all those who think  9 it's adequate, please raise your hand, for a yes  10 vote.  11       All those that think it's  12 inadequate, for a no vote, please raise your  13 hands.  14       Please state your name.  15       Dr. Talamini, why don't you start?  16       DR. TALAMINI: Talamini, no.  17       DR. EPSTEIN: Epstein, no.  18       DR. LINCOFF: Lincoff, no.  19       MR. HENNESSY: Hennessy, no.  20       DR. BUCHMAN: Buchman, no.  21       DR. KRAMER: Kramer, no.  22       DR. CHANG: Chang, no.</p>	<p style="text-align: right;">372</p> <p>1       DR. LINCOFF: That's easy. This is  2 the situation we all wish we were in, is knowing  3 the risks prospectively beforehand. I mean, I  4 think for short-term trials as well, for any  5 trial it's fairly clear that we want to  6 prospectively, not passively, but actively  7 gather cardiovascular endpoints, and cancer and  8 fractures, but particularly cardiovascular. By  9 accepted definitions to do that, not by adverse  10 event reporting, but by, at routine visits, a  11 follow-up to explicitly ask patients, and then  12 to fill in more detail as we typically do in  13 cardiovascular trials if a positive response, or  14 if there are triggers to suggest that there was  15 an event.  16       And for short-term studies, that  17 that follow-up be for at least 30 days after  18 the last administration of drug. And for  19 long-term studies, one could argue three to  20 six months, depending upon how long term  21 after the last administration of drug.  22       DR. BUCHMAN: Are you suggesting a</p>
<p style="text-align: right;">371</p> <p>1       DR. RICHARDSON: Richardson, no.  2       MS. CORKERY-DELUCA: DeLuca, no.  3       DR. LEVINE: Levine, no.  4       DR. PASRICHA: Pasricha, no.  5       DR. KRIST: Krist, no.  6       DR. CULLEN: Cullen, no.  7       DR. ROSING: Rosing, no.  8       DR. BUCHMAN: All those abstaining,  9 please raise your hand. State your name.  10       MR. PROSCHAN: Proschan, abstain.  11       DR. BUCHMAN: Are we going to announce  12 the vote here?  13       MS. PHAN: We have no yes, 14 no, and  14 I abstain.  15       DR. BUCHMAN: We're going to move on  16 to the final question of the day. This is a  17 non-voting question. Based on currently  18 available data, how should safety monitoring be  19 enhanced for patients enrolled in future  20 short-term and long-term clinical trials with  21 alvimopan?  22       Dr. Lincoff?</p>	<p style="text-align: right;">373</p> <p>1 formal Phase IV trial?  2       DR. LINCOFF: To me, Phase IV -- the  3 definition of Phase IV varies from person to  4 person.  5       Some mean it to say drugs approved,  6 and so any trial you do from that point on is  7 Phase IV, even if it's randomized. And if  8 that's the case, then, yes.  9       But if we're talking about, for  10 example, another indication, the OBD  11 indication, is that Phase IV or is that  12 Phase III? Because it's a different  13 indication. I don't know. But I'm talking  14 about in a randomized trial format, any trial  15 that is ever done from this point forward.  16 And certainly none of us have seen the data  17 for OBD, but if one were to want to come  18 forward with an indication for the OBD, one  19 would probably want better data than exists  20 already, no matter how good the efficacy  21 signal is.  22       DR. BUCHMAN: Dr. Pasricha?</p>

<p style="text-align: right;">374</p> <p>1 DR. PASRICHA: I just wanted to  2 clarify this because, I mean, are we talking  3 about studies required for approval or  4 post-approval studies? I'm not sure whether  5 this is linked to the previous question.  6 DR. KORVICK: I think it's now after  7 you've given your answers that you've given and  8 where we find ourselves today. We've had a  9 wide-ranging discussion on a lot of issues. So  10 this is your opportunity for each one of you, if  11 you feel, to register in what area you would  12 like to see what works. So it could be short  13 term, if you still think they need to do  14 something. It could be longer term, as someone  15 else said. So if you could just qualify what  16 you mean, and we'd find any advice helpful.  17 DR. BUCHMAN: And Dr. Lincoff has  18 suggested two very different mechanisms, one  19 being a Phase IV study on this particular  20 indication. Should this drug be approved in  21 this particular population? And the second  22 being, either in addition or instead of that,</p>	<p style="text-align: right;">376</p> <p>1 DR. LINCOFF: I'd like to add to those  2 last two comments because I think they're  3 excellent for several reasons. First of all,  4 these are groups which there still remains  5 equipoise, because we don't have data. So the  6 problem with doing pure Phase IV in the same  7 populations, of course, everybody says, well, I  8 already know it works, so how can I ethically  9 randomize to a placebo? And you could say it's  10 on the basis of safety, but it's much harder.  11 But if you expand the indications  12 to other groups for whom there is logic that  13 the high-dose narcotics would -- there would  14 be a benefit, you then truly have equipoise  15 and you could be focusing, for example, on  16 vascular surgery or elderly patients  17 undergoing orthopedic surgery. So that would  18 be a very good trial from the standpoint of  19 the science, the potential indication for the  20 company, because of expanding it, and the  21 opportunity to prospectively -- still in a  22 short-term study, because I don't know if</p>
<p style="text-align: right;">375</p> <p>1 for any future trials, Phase III or Phase II, in  2 other potential indications.  3 Dr. Talamini, you had a question?  4 DR. TALAMINI: I completely agree with  5 that. And I'm probably on thin ice here, but I  6 think consideration is doing -- expanding the  7 study to a group of patients that don't have  8 bowel resective surgery, but do require high  9 doses of narcotics postoperatively, and see what  10 the benefits and potential cardiovascular risks  11 might be in that population, where there may be  12 equal or even greater potential benefit.  13 MR. HENNESSY: I would recommend a  14 large randomized trial for cardiovascular safety  15 endpoints. That would probably be best  16 accomplished in a group at high risk for  17 cardiovascular outcomes, since the problem of  18 low numbers in the denominator won't be much of  19 an issue. Given the size of the potential  20 market, that should take relatively little time  21 to accumulate the number of patients.  22 DR. BUCHMAN: Dr. Lincoff?</p>	<p style="text-align: right;">377</p> <p>1 you're ever going to pursue OBD -- but in the  2 short-term study, gain much more data that  3 can then be extrapolated backward in terms of  4 cardiovascular safety.  5 DR. BUCHMAN: Dr. Levine? Okay, then  6 just turn your mike off.  7 Ms. DeLuca?  8 MS. CORKERY-DELUCA: Are you saying,  9 Dr. Lincoff, the 30-day trial that you had  10 mentioned before, to follow up with the 30 days?  11 What is your time limit?  12 DR. LINCOFF: Yeah, I was thinking 30  13 days after the last drug administration.  14 MS. CORKERY-DELUCA: Would this be  15 paid from the cost of the drug as it enters the  16 market? How is this going to be paid for?  17 DR. LINCOFF: These would be paid for  18 by the sponsor, who stands to make a profit in  19 the future.  20 MS. CORKERY-DELUCA: That's what I'm  21 asking.  22 DR. BUCHMAN: Dr. Krist?</p>

<p style="text-align: right;">378</p> <p>1 DR. KRIST: I was just saying, I'd be  2 able to do the study you were talking about,  3 randomizing people for the postoperative  4 indication on the PCAs with equipoise. Because  5 to me, there's still enough of a question  6 that -- and I as a patient would be willing to  7 be randomized for that. Because that's an  8 important question that effects the overall  9 risk-to-benefit ratio.  10 DR. BUCHMAN: Dr. Proschan?  11 MR. PROSCHAN: Proschan. Yeah, I  12 think the problem with doing a trial in people  13 who are at high cardiovascular risk is that if  14 you show that there is a problem, then that  15 doesn't answer the question for those who aren't  16 at high cardiovascular risk. Now, I know  17 Dr. Lincoff believes that it will not come out  18 that way and that may very well be true, but I'm  19 just saying if it does come out that way, then  20 there's still an open question for people who  21 aren't at high cardiovascular risk, is it fine?  22 DR. PASRICHA: And I'll have a very</p>	<p style="text-align: right;">380</p> <p>1 payoff for the company and the motivation to  2 do it, is to expand the indication. Because  3 otherwise, there's no motivation. All they  4 can do is downside. If a drug's approved and  5 then they're going to do another study in the  6 same indication, then all they can do is  7 lose.  8 But if you have the potential for  9 expanding an indication and you have both  10 low- and high-risk patients, you get science,  11 you get safety data, and they potentially get  12 a reason to sponsor a study. So I think if  13 you -- I mean, it's not straightforward, but  14 if you think about it, you could probably  15 satisfy all the criteria for a good design of  16 another study and still get some information  17 that we need.  18 DR. BUCHMAN: Dr. Hennessy?  19 MR. HENNESSY: The flipside of that  20 is, if the drug is used extensively for  21 off-label purposes, then the company gets its  22 cake and eats it, too, because they don't have</p>
<p style="text-align: right;">379</p> <p>1 hard time getting that study approved through an  2 RB using a drug for which a stated  3 contraindication is high-risk cardiac already  4 for your first approval. So I think you're  5 going to have to structure it in a way that gets  6 around -- assuming this is a post-approval  7 study.  8 DR. BUCHMAN: Dr. Lincoff?  9 DR. LINCOFF: First, I didn't know  10 that we were going to suggest that the  11 contraindication to the use of drug would be  12 high cardiovascular risk, because I don't know  13 that we've seen that. The cardiovascular risk  14 was not a prerequisite, or did I miss it in the  15 inclusion/exclusion criteria for entry into the  16 trial?  17 But that aside, I would think that  18 if you properly designed a trial with perhaps  19 stratification according to whether or not a  20 patient is at high risk and set a criteria,  21 but enroll both high- and low-risk, again the  22 issue is other surgeries. So there's the</p>	<p style="text-align: right;">381</p> <p>1 to do the studies to show that it's safe and  2 effective in the other groups, but they get the  3 sales because of the off-label use, which, my  4 prediction is likely to happen.  5 DR. BUCHMAN: It looks like we're  6 going to finish early. So because we do have a  7 few extra minutes here I want to see if anybody  8 from the committee has any additional questions,  9 either for the sponsor or for the FDA, or just  10 some comments they want to make themselves.  11 If not, I'm going to give a brief  12 chair summary of the six questions that we  13 had.  14 The first question was a non-voting  15 question. For the assessment of efficacy of  16 clinical trials of postoperative ileus, GI-2  17 and GI-3 have been used to measure times for  18 recovery of upper and lower GI function.  19 What do you consider a minimum acceptable  20 treatment difference, as measured by GI-2,  21 GI-3, for alvimopan relative to placebo?  22 The committee felt that either a</p>

<p style="text-align: right;">382</p> <p>1 12- or 24-hour difference was considered to  2 have clinical efficacy, and that GI-2 and  3 ready for discharge were the most important  4 endpoints.  5 This also included Question No. 2,  6 which was, do you consider the efficacy  7 results from the submitted POI studies to be  8 clinically meaningful?  9 So Question No. 3 was based on  10 currently available data. Do you have  11 concerns for the use of alvimopan  12 12-milligram capsules in the short term use,  13 that is the seven days or 15 doses, for  14 patients following partial large or small  15 resection surgery with primary anastomosis  16 with regard to the cardiovascular events,  17 neoplastic events, and bone fractures?  18 The committee felt that there was  19 some concern for the cardiovascular risks,  20 although these risks were not adequately  21 addressed. But certainly there was some  22 potential concern. The major concern was</p>	<p style="text-align: right;">384</p> <p>1 especially if the patients were not on  2 opiate. Although the consensus of the  3 committee was that there were benefits, even  4 if these benefits were relatively marginal  5 and mostly financial.  6 There is a potential for risk.  7 There was some concern expressed in the  8 committee that these risks might be real,  9 although might not be applicable to short  10 term use.  11 It was fairly unanimous that there  12 was small benefit and small risk, although  13 the risk was not zero.  14 Question No. 5, if alvimopan is  15 approved for the POI indication, do you  16 believe Adolor Corporation's proposed risk  17 management plan is adequate to address the  18 potential risks?  19 The unanimous decision of the panel  20 was that the risk management plan was not  21 adequate at all. However, it was also  22 brought up as to whether a risk management</p>
<p style="text-align: right;">383</p> <p>1 that follow-up was inadequate. Cumulative  2 dose might be important, especially with  3 repeated doses, but we have no data to either  4 support or deny that.  5 Risk analysis for the most part was  6 based on a single long-term study, and there  7 appeared to be weak signals for these three  8 problems. Nevertheless, the cardiovascular,  9 neoplastic, and bone risks cannot be  10 discounted. And that if the drug was  11 approved, there was clear opinion on the  12 committee that some sort of process would  13 need to be put in effect to be able to  14 monitor these specific potential side  15 effects.  16 Question No. 4 was, do you believe  17 the overall benefits of treatment with  18 alvimopan outweigh the potential risks for  19 short-term in-hospital use in patients  20 following large or small bowel resections?  21 There was some concern with  22 efficacy as demonstrated in the trial,</p>	<p style="text-align: right;">385</p> <p>1 plan was even really necessary and whether,  2 if the drug was approved, such a plan should  3 be oriented towards more specific prevention  4 of off-label use.  5 And finally, Question No. 6, based  6 on currently available data, how should  7 safety monitoring be enhanced for patients  8 enrolled in future short-term and long-term  9 clinical studies of alvimopan?  10 It was the general consensus of the  11 committee that prospective longer term safety  12 monitoring studies for adverse events would  13 be necessary. These could take the form of  14 one of two mechanisms: either A, a Phase IV  15 type trial to monitor the risk-benefit  16 ratio -- or I should say, just the risks of  17 these specific and perhaps other potential  18 events in patients that end up receiving the  19 drug; or to implement a more thorough and  20 long-term follow-up in any future studies for  21 potential future indications.  22 So with that, I'm going to adjourn</p>

1 our meeting. Thanks for coming.  
2 (Whereupon, at approximately 4:09  
3 p.m., the MEETING was adjourned.)  
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<b>A</b>				
<b>abdomen</b> 28:7	339:2 352:8	<b>accumulating</b>	36:13 259:2	<b>Additionally</b>
<b>abdominal</b>	371:10,14	119:6	269:22	164:19 180:8
17:20 22:22	<b>abstained</b>	<b>accumulation</b>	<b>acts</b> 210:3	<b>address</b> 24:11
28:6,8 30:6	329:20	66:6 67:13	<b>actual</b> 43:8	60:22 78:11
31:1,5 40:7	<b>abstaining</b>	<b>accurate</b> 122:11	121:16 122:5	85:3 93:16
41:3 62:12	306:17 371:8	<b>achieve</b> 44:19	124:22 199:13	94:6 98:11
78:19 79:12,16	<b>abstains</b> 307:3	95:11 140:5	248:6,8 252:13	100:3 103:22
111:18 135:17	<b>abstention</b>	141:8,22	293:16	173:1 182:3,5
137:14,21	306:20,21	142:14 173:8	<b>acute</b> 22:10	199:5 211:11
221:5,21	<b>abstentions</b>	174:22 237:21	24:18 62:5	211:15 213:17
296:20 297:2,7	329:18	<b>achieved</b> 39:2	87:15 166:16	218:8,9 219:5
314:15	<b>academic</b>	50:10 54:6	178:12 180:18	220:1,4 229:2
<b>aberration</b>	131:19 133:1,7	55:2 58:21	181:5,6 225:1	236:10 238:6
169:3,6	289:15	60:1 113:18	225:11 281:18	241:17 246:7
<b>ability</b> 68:11	<b>accelerate</b> 16:18	189:13 254:15	359:12	249:11 256:4
115:6 262:9	<b>accelerated</b>	<b>achieves</b> 44:7	<b>add</b> 111:13	259:8 275:12
358:9,11 362:7	32:22 39:15	<b>achieving</b> 55:12	132:20 212:16	275:13 277:14
<b>able</b> 95:15 96:3	60:3 91:3	59:19	243:22 286:5	308:5 327:4
96:5 97:9	101:9	<b>acid-induced</b>	296:15 303:15	352:14 353:15
128:11 129:4	<b>accelerating</b>	209:16	323:5 348:22	367:19 370:1
181:6 194:1	41:17	<b>acknowledged</b>	376:1	384:17
203:19 246:20	<b>acceleration</b> 8:6	304:11 312:17	<b>added</b> 220:14	<b>addressed</b>
246:21 247:3	13:9 33:5	<b>Act</b> 7:3,4 11:5	361:10,10	212:15 246:11
247:12 262:10	59:11 90:15	11:16 12:7	<b>addicts</b> 361:20	308:12 310:19
286:3 288:8	100:22 135:9	13:18	<b>adding</b> 191:10	334:3 382:21
324:11 362:15	143:20 146:8	<b>acting</b> 21:18	347:5	<b>addresses</b> 179:9
362:17 367:1	<b>accept</b> 317:14	36:11 37:8	<b>addition</b> 15:11	179:18 219:8
378:2 383:13	<b>acceptable</b>	208:13	25:22 40:8	242:18
<b>abnormalities</b>	144:3 183:12	<b>action</b> 35:12,18	70:3 76:11	<b>addressing</b>
229:20	284:10 381:19	36:1 75:2 85:1	82:3 85:15	356:7 366:20
<b>ABRAHAM</b> 3:8	<b>accepted</b> 246:16	88:10 99:9	86:19 88:21	<b>adequacy</b> 83:1
<b>abrogating</b>	372:9	116:3 136:9,19	89:21 91:2	<b>adequate</b> 117:1
220:12	<b>accepting</b> 198:9	167:15 172:21	113:22 151:19	256:4 312:3
<b>abscess</b> 105:12	<b>access</b> 90:8	173:4 210:4	166:12 170:3	338:5 352:13
<b>absence</b> 28:5	175:5 177:17	360:6,19 361:2	187:13 224:12	352:22 353:13
65:9 361:8	<b>accident</b> 150:4	361:4	266:1 273:15	353:18 355:19
<b>absolute</b> 255:15	<b>accommodated</b>	<b>actions</b> 112:5	374:22	356:7 365:12
<b>absolutely</b> 132:9	360:18	<b>activation</b> 99:19	<b>additional</b> 27:9	368:16 369:9
132:22 282:22	<b>accomplished</b>	<b>active</b> 36:6 38:4	30:18 45:11	369:12,17
327:18	375:16	102:12 103:16	47:17 48:9	370:1,5,9
<b>absorbed</b> 275:2	<b>account</b> 252:9	135:7 166:20	69:22 71:12	384:17,21
<b>absorption</b>	<b>accounted</b>	168:21 169:5,9	80:13,17	<b>adequately</b>
116:17 166:13	110:13	172:9 199:18	130:16,18	152:19 166:3
208:17,21	<b>accrued</b> 133:5	311:10 321:3	137:3 140:21	246:20 308:12
<b>abstain</b> 304:10	<b>accumulate</b>	<b>actively</b> 323:6	158:7 212:17	382:20
305:7 330:2	367:2 375:21	372:6	250:5 266:6,8	<b>adhesions</b>
	<b>accumulated</b>	<b>activities</b> 14:11	332:4 360:4	314:13
	261:19	<b>activity</b> 13:21	381:8	<b>adjourn</b> 385:22

<b>adjourned</b> 386:3	<b>admit</b> 333:16	385:12	<b>agenda</b> 13:5,13	320:1
<b>adjudicate</b> 80:17	<b>admittedly</b> 192:10	<b>adversely</b> 31:19	15:18	<b>alert</b> 87:22
<b>adjudicated</b> 117:12 118:1,3 198:3,10,18,19 199:21 200:13 202:10 222:12 222:15,20 223:15,18 225:21 228:4 228:11 320:6 350:8	<b>Adolor</b> 5:5,6,15 5:16 13:7 17:10 20:12,15 22:5,9 24:14 25:2 35:5 60:19 80:16 81:22 82:3 94:5 213:16 236:9 259:10 261:15 268:13 281:12 352:12 368:15 369:21 384:16	<b>advertising</b> 176:10	<b>agent</b> 21:13 34:21 70:13 74:1	180:19,20 181:16,18
<b>adjudication</b> 81:16 117:10 118:7,10 119:19 198:12 200:18,21 202:16	<b>Adolor's</b> 35:2	<b>advice</b> 18:11 374:16	<b>agents</b> 29:3 270:15	<b>Alex</b> 8:21
<b>adjudications</b> 117:6	<b>advance</b> 342:21	<b>advise</b> 16:1	<b>aggressive</b> 111:17 246:17 247:7	<b>Alexander</b> 3:4 4:16 26:2 256:5,8,8
<b>adjusted</b> 267:5,9	<b>advanced</b> 73:2 74:4 164:16	<b>advisory</b> 1:7 7:3 7:4,12 10:21 11:3,4 16:11 71:1	<b>aggressively</b> 103:9 108:8	<b>algorithm</b> 359:18
<b>adjusting</b> 124:5	<b>advancement</b> 33:5 40:1	<b>advocacy</b> 196:10	<b>ago</b> 276:7 349:2	<b>allayed</b> 310:15
<b>adjustment</b> 124:10	<b>ADL</b> 166:21	<b>advocate</b> 348:11	<b>agonism</b> 308:7	<b>Allergy</b> 3:11 9:2
<b>ADL</b> 166:21	<b>advantage</b> 27:22 108:20 227:9 253:2	<b>aero-digestive</b> 75:14	<b>agonist</b> 116:5	<b>alleviate</b> 226:15 241:15
<b>administer</b> 178:9	<b>advantageous</b> 221:14	<b>AEs</b> 146:21	<b>agonists</b> 77:4	<b>allot</b> 130:17
<b>administered</b> 37:19 94:21 108:16 126:17 130:11 178:10 178:12 281:20	<b>adverse</b> 19:8 21:7,20 38:3,5 38:11 44:10 50:7 51:8 64:6 66:20 67:3 69:4,20 70:19 71:12 75:8 79:4,6,13 80:1 80:3 81:17 83:2,9,14 85:20 89:7 110:21 119:14 119:22 136:21 145:12,21 146:1,5,6 164:4 168:13 172:14 230:6 254:17 273:12 273:20,22 274:1 311:8 345:9 372:9	<b>affairs</b> 2:20 20:17,20	<b>agranulocytosis</b> 174:16	<b>allow</b> 44:18 101:6 127:5 157:8 212:15 212:19 238:6
<b>administering</b> 177:22 276:2 294:13		<b>affect</b> 19:21	<b>agree</b> 124:14 139:4 190:5 193:7 273:3 299:18 303:4 305:11 324:10 324:21 333:5 333:14 342:3 343:14 353:7 354:7 357:11 357:17 358:2 358:14 366:19 367:17 375:4	<b>allowed</b> 6:22 72:19 100:16 228:21 312:8 314:2
<b>administration</b> 1:1 3:18 4:2 11:1 29:9 31:17 78:1 195:5,7 208:22 220:8 280:4 372:18,21 377:13		<b>afford</b> 12:11	<b>agreed</b> 18:3 23:6 65:7 296:18	<b>allowing</b> 48:10 176:20
<b>administrative</b> 32:6		<b>afraid</b> 346:7	<b>agreement</b> 42:18 71:5 178:17 368:17	<b>allows</b> 14:14
<b>admission</b> 106:18		<b>afternoon</b> 130:17 188:1 193:15 194:12 194:16 211:3 289:19 322:9	<b>agreements</b> 177:13 180:15	<b>all-cause</b> 90:22 104:3,11 149:19 154:16
		<b>agency</b> 23:6,20 24:10 80:12,16 140:20 172:17 179:18 183:3 194:1 196:4 203:21 283:19 305:9 350:22 368:17	<b>agrees</b> 122:21	<b>alteration</b> 234:16
		<b>agency's</b> 12:4 14:21 61:1 184:6	<b>ah</b> 124:21	<b>alternative</b> 107:20 227:12 335:5
			<b>ahead</b> 248:11 254:1 298:10 298:12 303:13 350:19 369:14	<b>alternatively</b> 47:14
			<b>air</b> 304:6	<b>altogether</b> 128:3
			<b>al</b> 82:8	<b>alvimopan</b> 8:5 13:6 16:16 19:20 21:18 33:19 34:6 35:8,20 36:4,8 36:10,13,17 37:1,12,17 38:12 39:6 41:16,21 44:18 50:16 51:6 52:20 53:2,11
			<b>Alan</b> 2:3 6:5 278:4	
			<b>albeit</b> 319:16	

53:19 54:15,19 55:2,8,14 57:4 57:14 58:14 59:1,4,8 60:5,8 60:16 61:10 62:10,13,18 63:19,22 65:8 65:12,18 66:4 67:2,16 68:21 69:6,11 72:11 72:16,17 73:17 74:2,3,6,10,15 76:12,19 78:1 78:3,21 79:9 80:7 81:2,8 84:8,14,18 91:22 94:3 96:15 98:18 101:2 107:19 108:21 110:18 111:2 119:8 124:16 128:22 129:4 134:11 134:12,15 135:1,3 137:2 140:4 141:7,21 142:13 144:5 144:16 145:10 145:13,17 146:2,6,7,14 146:22 148:19 149:15 150:18 151:15 153:16 154:1,19,22 155:4,9,12 156:12 158:1 158:13 159:5 159:18,19,21 160:9,13 161:1 162:18 163:6 163:13,21 164:13 165:3 165:13 166:2,3 166:9,20 167:4 167:10,19 168:1,11,21 169:4 170:10 171:17 172:1,3	172:9,13 173:2 179:8 182:22 209:7 215:15 215:19 225:18 226:5 229:18 234:8 237:11 242:14 250:1 252:18 255:14 255:20 256:22 262:9 265:5,15 267:7 271:2 284:11 307:8 327:22 331:12 336:13 351:2 352:11 369:20 371:21 381:21 382:11 383:18 384:14 385:9 <b>alvimopan's</b> 35:12 36:1,21 42:11 45:12 46:18 94:20 <b>alvimopan-tre...</b> 51:13 157:17 158:10 161:10 <b>ambulation</b> 33:6 39:21 <b>ameliorate</b> 303:19 <b>America</b> 2:15 48:6 <b>American</b> 39:7 42:22 44:6 46:1,6,14 48:13,16 49:2 49:11,18 50:18 50:19 52:13 56:8,14 58:5 59:3 60:1,4 81:18,19 83:15 142:13,20 143:11 192:19 193:5 258:9 <b>Ames</b> 169:1,6 <b>amount</b> 95:19 177:7 253:7 <b>amounts</b> 295:18 <b>analgesia</b> 29:16	29:21 33:7 37:3 40:10 59:2 62:6 63:2 72:9,13 84:14 108:10 293:21 335:4 <b>analgesic</b> 21:22 <b>analgesics</b> 29:8 36:18 37:5 40:19 48:18,21 <b>analyses</b> 43:20 48:9,11 82:4 150:12 156:7 198:16 202:15 202:16,16 204:18 211:21 212:5 216:16 223:7 257:6 <b>analysis</b> 38:19 43:1 46:7 47:4 47:19 66:1 67:8 68:19 73:19 74:5 81:11,22 95:1 117:16 134:5 150:20 155:7 159:2 160:1 163:19 164:3 183:20 196:17 197:20 199:3 203:6 204:20 204:22 224:10 235:16 239:19 253:18 254:4 254:10,13,14 264:6 272:3 334:13 344:21 348:7 383:5 <b>analyze</b> 68:11 104:6 217:21 <b>analyzed</b> 158:6 216:12 223:20 <b>anastomosis</b> 8:9 13:12 16:21 27:19 40:7 45:4 92:22 94:9 135:12 245:1,7 307:12	328:4 331:15 351:5 382:15 <b>anastomotic</b> 27:22 105:9,10 244:19 <b>and/or</b> 27:16 135:17 307:14 328:6 <b>anesthesia</b> 37:20 <b>anesthesiologi...</b> 261:20 <b>anesthetics</b> 29:1 <b>anesthetized</b> 167:22 <b>aneurism</b> 221:22 <b>Angeles</b> 2:6 <b>angina</b> 150:4 203:8 224:13 225:5,12 320:8 <b>animal</b> 171:18 270:8 <b>animals</b> 259:4 <b>Annapolis</b> 257:16 <b>Anne</b> 2:8 <b>announce</b> 283:21 371:11 <b>announced</b> 125:22 <b>annually</b> 27:3 <b>answer</b> 26:2 94:7,17 107:3 108:2 116:10 127:2 129:20 184:8 189:10 191:20 195:15 210:5,12 218:7 226:8,19 229:3 233:1 246:11 254:9 262:13 263:17 267:17 267:21 272:10 272:15 277:9 281:14,14 297:22 315:5 339:14 344:1 346:5 354:14	366:10 367:16 378:15 <b>answered</b> 339:13 <b>answering</b> 298:21 <b>answers</b> 120:21 133:11 233:6 374:7 <b>antagonism</b> 99:10 <b>antagonist</b> 21:19 36:5 37:8 94:18 135:3 215:20 269:14 <b>antagonists</b> 62:9 75:4 77:5 269:19,22 <b>Anthony</b> 5:13 26:15 213:19 <b>antibiotics</b> 276:2 364:5 365:20 <b>anticipated</b> 245:14 <b>antiemetics</b> 228:21 229:4 229:13 <b>anti-platelet</b> 187:14 <b>anxious</b> 7:10 <b>anybody</b> 109:17 307:16 336:10 337:11 347:14 357:20 381:7 <b>anymore</b> 226:21 <b>aortic</b> 221:21 <b>apart</b> 71:2 111:10 251:2 <b>apologize</b> 130:21 249:20 281:16 <b>apparent</b> 119:5 150:16 161:16 162:17 <b>apparently</b> 71:19 316:21 <b>appear</b> 132:4 <b>appeared</b> 157:2
---	---	---	---	--

160:19 280:6 320:2 383:7 <b>appearing</b> 119:7 <b>appears</b> 38:16 74:18 155:7 157:7 163:22 237:13 <b>applicability</b> 109:3 <b>applicable</b> 109:5 384:9 <b>application</b> 13:7 108:10,13 247:22 <b>applied</b> 44:5 88:11 <b>applies</b> 241:22 <b>apply</b> 132:2 278:11 302:13 303:7 310:1 360:15 <b>approach</b> 43:11 46:17 88:10 97:8 315:15 354:9 <b>approached</b> 326:15 <b>approaches</b> 33:13 294:3 <b>appropriate</b> 84:7 85:7 88:14 89:22 91:22 99:3 113:14 114:13 124:18 175:20 176:16 187:20 201:2 237:16 243:17 295:15 360:12 <b>appropriately</b> 91:15 219:20 <b>approvable</b> 23:21 24:8 85:1 136:18 <b>approval</b> 20:5 24:17 136:8 140:21,22 172:1 196:9,12	321:15 364:7 365:14 374:3 379:4 <b>approved</b> 17:1 33:10 34:10 85:13 89:19 93:11 135:20 213:4 322:17 347:11 349:3 352:11 354:10 363:2 366:11 369:20 373:5 374:20 379:1 380:4 383:11 384:15 385:2 <b>approves</b> 355:1 355:1 <b>approximately</b> 49:8 50:2,4 54:14 56:6,10 56:15 57:11,17 58:18 63:11 72:16 79:1 96:9 125:3 232:19 386:2 <b>approximates</b> 72:1 240:1 <b>April</b> 137:1 <b>arbitrary</b> 251:9 266:15 <b>area</b> 47:10,11 210:19 250:18 251:22 252:3 288:14 290:21 297:8 356:3 374:11 <b>areas</b> 165:15 <b>arena</b> 103:8 <b>argue</b> 274:12 340:13 372:19 <b>argument</b> 287:3 323:17,18 331:22 332:1 <b>arm</b> 74:3 253:9 321:3 <b>arms</b> 253:9 306:1 <b>arrest</b> 150:7	224:15 <b>arrhythmia</b> 150:6 323:19 <b>arrhythmias</b> 122:1 308:8,9 309:13 315:21 315:22 316:5 <b>arrives</b> 348:15 <b>arteries</b> 207:15 <b>article</b> 107:14 <b>article's</b> 107:14 <b>Arundel</b> 2:8 <b>ASA</b> 40:4 <b>ascertain</b> 105:5 180:6 <b>ascertainment</b> 64:14 68:15 <b>aside</b> 379:17 <b>asked</b> 23:21 26:19 80:12 83:13 101:16 195:20 228:1 244:7 267:18 269:16 285:16 312:13 324:9 324:21 334:12 344:20 <b>asking</b> 24:8 227:19 230:17 249:2 280:13 295:1,3 356:1 377:21 <b>asleep</b> 289:7 <b>aspect</b> 93:8 <b>aspects</b> 92:20 <b>aspiration</b> 106:19 <b>assay</b> 167:10 169:2,6,6 <b>assays</b> 76:14 <b>assess</b> 31:15 70:18 72:10 101:6 139:6 152:19 175:16 185:18,19 189:18 195:4 262:9 <b>assessed</b> 38:3	41:15 59:2 65:2 71:1 83:16 152:14 <b>assessing</b> 63:19 97:16 194:17 198:5 <b>assessment</b> 42:11 46:13 65:16 73:14 74:20 81:10 144:9 150:15 175:14 284:5 381:15 <b>assessments</b> 76:12 152:6 <b>assigned</b> 72:20 224:9 <b>assigning</b> 270:19 <b>assignment</b> 225:9 <b>assist</b> 176:14 <b>associated</b> 21:10 28:3 30:2,11 30:13,17 32:4 41:7,12 42:9 46:20 54:9,22 58:6,9,11,14 59:12 61:21 70:20 75:14,17 77:3 90:18 115:18 147:7 266:8 267:3 316:10 <b>association</b> 67:1 75:7 76:5 81:19 119:7 <b>assume</b> 94:11 230:1 <b>assuming</b> 379:6 <b>assumption</b> 179:20 <b>assure</b> 364:13 <b>assuring</b> 357:10 <b>ate</b> 289:3,4,4,6 <b>atelectasis</b> 31:8 <b>atherosclerosis</b> 319:7 <b>atrial</b> 364:4	<b>attempt</b> 94:22 361:19 <b>attempts</b> 197:10 <b>attend</b> 15:10 <b>attendance</b> 15:13 <b>Attendees</b> 4:15 5:2 <b>attention</b> 37:11 48:2 78:10 92:4 172:19 330:15 <b>attest</b> 182:9 <b>attestation</b> 177:11 182:12 <b>atypical</b> 70:12 <b>at-hand</b> 199:4 <b>audience</b> 7:17 90:1 <b>August</b> 136:2 137:5 <b>Australia</b> 137:16 268:9 <b>authority</b> 11:4 <b>authorized</b> 12:1 12:8 <b>autonomic</b> 28:16 <b>available</b> 15:2 26:1 33:11 77:16 85:14 86:2 87:4 120:6 136:6 165:7 181:17 225:15 238:17 273:19 307:7 327:21 357:20 371:18 382:10 385:6 <b>average</b> 49:6,8 63:1 149:8 164:15 239:22 253:7,15 285:10,17 317:8 <b>averaging</b> 252:8 252:11 <b>avoid</b> 128:3
---	---	--	---	---

174:14	<b>based</b> 13:13 18:9	175:15	333:15,18	84:2 143:7
<b>avoidance</b> 30:21	43:5,22 47:7	<b>behaviors</b>	334:1,21 337:3	151:10 173:10
<b>avoids</b> 43:9	52:12 74:16	175:21	337:5 338:2	174:21 201:18
<b>aware</b> 7:9 90:5	76:3 94:11	<b>Beitz</b> 3:19 10:12	344:10,16	252:16 316:16
269:15,18	108:3 116:14	10:12 211:18	346:1 348:14	317:22 318:3
271:6,14,16	126:9 139:11	<b>belief</b> 244:17	349:6,15 351:7	343:2,8 348:15
<b>a.m</b> 6:2 56:16	140:19 185:6	<b>believe</b> 60:9 75:6	357:5 361:9	357:13
300:6,9	186:2 198:1	84:5,16 91:19	375:12 376:14	<b>BID</b> 38:20 138:9
	235:15,18	93:5 97:15	384:12	147:18,19
	250:6 254:14	98:12,13	<b>benefits</b> 25:10	<b>big</b> 202:11
<b>B</b>	265:20 299:6	109:20 110:11	30:1 41:8	225:10 290:22
<b>back</b> 20:11 78:6	299:13 307:7	111:16 112:2	90:18 177:19	308:16 341:16
78:10 120:8,20	312:9,11	115:11 122:21	178:20 179:3	342:20 350:15
121:19 125:8	315:11 321:11	128:17 130:1,7	331:11,20	353:13
133:14 193:16	324:13 327:21	136:5 187:16	337:1 338:5	<b>bigger</b> 278:16
204:3 205:11	335:14 350:17	192:21 197:3,9	339:11 342:4	295:17 366:8
205:15,17	371:17 382:9	215:17 217:2	346:21 348:16	<b>biggest</b> 214:10
210:17 218:21	383:6 385:5	222:7 243:13	351:1 360:12	244:3 365:3
220:2 242:10	<b>baseline</b> 64:4	244:21,22	375:10 383:17	<b>bill</b> 32:10
247:18 250:18	120:13 160:17	250:2 254:11	384:3,4	<b>billing</b> 239:9
254:22 257:17	164:15 214:21	274:2,12	<b>benefit-risk</b>	<b>bind</b> 29:9
267:20 273:8	215:7 221:22	275:18 277:5,7	24:19 84:17	<b>binding</b> 36:19
276:6 278:1	356:21	289:14 302:2	91:21 144:9	<b>bioassay</b> 170:14
279:13 314:7	<b>basically</b> 94:10	309:22 331:11	<b>benefit-to-risk</b>	<b>bioavailability</b>
321:16 330:11	139:1 229:16	332:16 351:1	344:21 346:7	135:4
339:14,15	253:3 274:4	352:12 357:15	<b>benign</b> 70:8	<b>biological</b> 28:15
347:18 355:7	289:9 301:3	363:3,4 369:21	157:21 158:18	64:22 269:13
<b>background</b>	346:12 364:16	383:16 384:16	271:14 301:2	270:4
17:10,16	364:22	<b>believed</b> 236:2	334:6,13	<b>biomarkers</b>
172:22 179:7	<b>basis</b> 180:22	<b>believes</b> 24:14	<b>best</b> 39:18	80:14
184:18 185:11	228:20 288:13	378:17	116:11 184:11	<b>Biostatistics</b>
287:6	316:8 332:9	<b>belly</b> 332:4	184:21 189:2	3:10 250:16
<b>backup</b> 193:14	376:10	<b>beneficial</b> 21:22	363:15 375:15	<b>bit</b> 112:5 117:15
<b>backward</b> 377:3	<b>battery</b> 166:22	77:1 128:11	<b>bet</b> 118:12	131:16 195:19
<b>balance</b> 31:14	168:22	288:18 345:14	<b>better</b> 27:20	197:2,22 203:2
70:19 234:6	<b>battle</b> 348:10	<b>benefit</b> 24:22	48:10 107:20	218:4 219:13
264:15,21	<b>beat</b> 114:2	27:21 41:1	109:2 112:18	233:14,18
359:20	<b>becoming</b> 366:8	45:8,12 47:19	184:22 185:6	236:13 260:22
<b>balanced</b> 73:11	<b>bed</b> 238:17,19	60:11 85:18	185:11 186:3	286:21 350:13
82:21 149:19	287:15,16	87:5 97:9	186:14 197:11	<b>black</b> 346:5,6
157:2 160:19	288:2,2,4,12	102:2 194:18	237:18 252:19	353:14
161:7 163:10	289:21 291:7	219:3 220:14	261:2 273:2	<b>blanket</b> 335:9
189:8	332:3	220:17 222:7	277:14 309:8	<b>blinded</b> 68:16
<b>balances</b> 361:8	<b>beg</b> 300:7	241:2 248:22	333:11 341:19	81:15 302:6,8
<b>ballot</b> 304:12	<b>beginning</b> 92:1	249:4,6 253:7	359:11,22	315:21
<b>bariatric</b> 2:19	162:4 261:3	258:13 271:21	361:7,19	<b>blip</b> 318:9,10
226:15 355:9	<b>begs</b> 303:12	277:6 312:7	362:19 373:19	<b>blister</b> 89:12
<b>barn</b> 355:8	<b>behavior</b> 116:15	332:15,22	<b>beyond</b> 66:5	<b>blizzard</b> 290:12
<b>barrier</b> 208:10				

<b>bloated</b> 332:4	270:3 340:7	248:4,5 255:8	258:5 276:16	234:10 235:2
<b>bloating</b> 28:6	<b>bound</b> 37:1	256:12 261:14	<b>broad</b> 70:17	239:4 240:22
<b>block</b> 29:11	154:4	286:8,14,16	95:22 102:22	244:14 247:14
87:17	<b>bowel</b> 8:8 13:11	288:1 298:2	103:14 194:8	253:10,22
<b>blockage</b> 308:8	16:20 17:21	307:11 314:12	218:14 265:6	254:2 255:18
<b>blocking</b> 21:21	19:15 21:5,16	328:3 331:14	<b>broader</b> 108:10	257:14 258:17
220:14 236:7	22:1,13,21	335:4,9,11	<b>Brodsky</b> 148:8	259:17 262:16
<b>blocks</b> 37:1	23:4,7 24:1,17	338:12 339:17	<b>broke</b> 258:6	263:7 271:11
<b>blood</b> 116:19,21	26:22 27:2,8	341:2 351:5	<b>broken</b> 104:11	272:14 275:7
117:1 174:18	27:14 29:19	356:12 365:2	104:18 154:6	276:6 277:9
259:1,3	30:20 31:2,11	375:8 383:20	154:16 163:2	280:10 283:16
<b>bloodstream</b>	34:20 35:10	<b>bowels</b> 289:19	<b>brought</b> 19:16	284:22 285:20
208:18	37:2 38:17	<b>bowel's</b> 244:22	118:11 277:14	286:6,18
<b>BMI</b> 164:15	39:8 40:6,17	286:12	278:4 317:1	288:20 290:2,4
<b>board</b> 103:17	42:4,12,17	<b>bowel-related</b>	333:6 335:19	291:2 292:4,12
123:18 219:1	44:16 45:3,5,7	194:3	336:11 384:22	292:17,21
229:7 287:8	45:10 46:13,15	<b>box</b> 346:5,6	<b>brunt</b> 358:12	294:16 295:9
310:9	48:6 49:22	353:14	<b>Buchman</b> 2:3	296:6,14
<b>Bob</b> 9:5	50:8,20,22	<b>brackets</b> 257:20	6:3,5 8:3 10:14	297:10,14,19
<b>body</b> 207:11	51:17,22 52:8	<b>brand-new</b>	16:4,10 20:11	298:9,12 299:7
208:5	52:11,13 53:18	290:14	20:14,21 26:14	300:2 303:3,11
<b>bone</b> 64:10	55:11 58:21	<b>break</b> 105:14	92:5 94:13	303:16,21
74:13 75:5	59:10 60:12	133:14 210:17	99:4 106:6	304:21 305:4
77:2 82:16	61:11,19 78:18	330:5,6,7,10	107:9 108:22	305:13,22
137:4 147:13	82:6,13 83:18	<b>breakdown</b>	112:3 115:16	306:4,4,6,15
164:1 168:10	84:19 85:18	223:9 233:16	118:16 121:2	306:22 307:4
168:10 170:18	89:17 90:1	<b>breaks</b> 7:8	125:22 126:7	308:13 310:4
307:14 310:6	97:17 100:6	316:15	127:17 128:13	310:20 313:4
313:10 319:4	101:1,7 109:4	<b>breast</b> 159:9	129:8 130:13	315:12 316:14
325:2,14 328:6	109:10 110:1	160:11	133:13,22	317:16 318:15
331:6 338:21	110:19 115:15	<b>brief</b> 16:13	183:17 186:9	322:5 323:10
339:4 382:17	119:10 122:19	35:11,15	187:6,22	323:15 324:4
383:9	123:4,17	249:13 264:2	190:17 192:8	325:10 326:13
<b>bones</b> 163:2	126:12 129:1,1	316:19 330:18	193:18 194:13	327:2,11,18
170:9	129:5,5,14	381:11	195:16 197:18	328:9,14 329:5
<b>book</b> 223:5	130:6 135:11	<b>briefing</b> 35:22	203:11 204:1	329:5,7,18,21
<b>borne</b> 115:13	137:13 138:2,4	47:4 49:20	205:2 207:1,6	330:3,14
267:15	138:20 145:4	73:20 128:17	208:1,16 209:1	332:17 333:4
<b>Boston</b> 119:2	145:17 146:11	191:17 309:12	210:8,16 211:3	333:13 334:4
269:6	147:4,6 148:18	<b>briefly</b> 24:11	212:11 213:13	335:13,17
<b>bother</b> 228:12	162:8 194:1	267:21	214:7 216:9	336:20 338:10
299:19	196:1 205:10	<b>bring</b> 103:22	217:14 219:7	341:4 342:6,13
<b>bothered</b> 309:10	205:20 206:17	108:1 114:18	219:12 220:18	343:13 344:17
<b>bothers</b> 293:17	215:6 221:5,10	228:8 238:5,18	221:19 222:9	346:9 348:1,22
344:3	226:7,15	245:3 317:2	226:10 227:14	350:4,19
<b>bothersome</b>	227:16 244:18	<b>bringing</b> 280:21	227:20 228:6	351:21 352:2,2
342:18	245:6,15,16	303:16	228:16 229:19	352:9 353:6,10
<b>bottom</b> 107:7	246:6 247:3	<b>brings</b> 24:13	230:8 233:20	353:16,20

354:6,18 355:13 356:10 357:7 358:19 361:11 364:15 365:9 366:12 367:12,14 368:10,21 369:3,14,18 370:8,20,20 371:8,11,15 372:22 373:22 374:17 375:22 377:5,22 378:10 379:8 380:18 381:5	<b>calendar</b> 43:15 57:21 <b>California</b> 2:6 10:2 92:13 <b>call</b> 6:4 8:10 151:5 152:10 212:20 289:5 307:15 341:9 <b>called</b> 18:6 175:4 288:21 323:13 <b>calls</b> 360:10 <b>Camm</b> 4:18 26:3 118:13,16,18 223:12,13 <b>Canada</b> 137:17 268:3,11 <b>cancelled</b> 15:13 <b>cancer</b> 5:3 26:7 34:3 50:4 52:6 73:9 74:17 84:10 153:4,11 154:12 157:12 159:9,9,11 160:13,15 161:19 162:1 162:13 203:13 203:15,15,16 204:7,9,12,16 236:3 262:18 263:3,21 265:14 269:5,6 269:9,11,14,17 270:6,17 271:3 271:9 277:21 278:17 279:17 279:19 282:21 297:6 326:18 326:19 357:1,2 372:7 <b>cancers</b> 75:15 160:9,11 266:21 270:13 283:3 <b>cancer-related</b> 61:18 72:8,12 159:13 203:19 <b>canine</b> 167:13	<b>Cannon</b> 119:1 <b>capsule</b> 86:17 <b>capsules</b> 20:18 307:9 328:1 382:12 <b>capture</b> 196:19 <b>captured</b> 32:9 273:21 <b>carcinogen</b> 171:19 <b>carcinogenic</b> 70:14 <b>carcinogenicity</b> 76:14 167:1 169:10,17 172:10 270:10 271:8 <b>carcinoma</b> 159:9 <b>cardiac</b> 76:9,10 80:14 150:6 224:15,15 309:14 311:11 323:19 347:7 350:7,15 356:5 379:3 <b>cardio</b> 355:3 <b>cardiologist</b> 26:3,4 315:13 317:13 348:5 <b>cardiologists</b> 119:1,21 318:18 348:10 350:9 <b>cardiology</b> 3:15 81:14,19 111:21 316:11 <b>cardiotoxicity</b> 76:8 <b>cardiovascular</b> 3:8 64:9 65:6 65:19 66:5,15 67:9,13,22 68:11,17 69:2 69:11,16 75:13 76:6,20 77:2 80:15,18 81:1 81:5,16 84:10	85:3 109:8,11 109:13 110:5 110:16,16,21 110:22 111:20 115:21 117:6,9 117:18 119:11 119:18,22 120:11,14,17 121:20 131:1,5 131:8,10 132:16 136:14 136:21 137:3 147:12 148:15 149:4,5,13,16 149:18,21 150:1,5,7,13 150:17 152:12 152:17,20,22 153:13,16 154:2,14,15 156:6 165:15 166:10 167:9 167:18,22 172:3 179:9,19 179:21 180:6 180:11 181:21 187:10 192:7 194:20 195:4 195:22 196:2 196:11,16 197:21 198:2 198:13 199:14 199:20 200:5 200:11 201:3,6 201:11,13 211:17 212:3 214:21 222:1 222:18 225:19 226:4 228:15 230:10 231:11 234:4 249:3 256:13 257:1 268:17 307:13 307:22 308:2 310:14,18,22 314:22 315:18 316:8 318:17 319:6 322:4	323:7 324:10 325:9 327:17 328:5,7,15,17 331:4 333:22 338:19 339:10 347:3 353:4,8 353:22 357:1 360:5 362:18 362:22 364:20 372:7,8,13 375:10,14,17 377:4 378:13 378:16,21 379:12,13 382:16,19 383:8 <b>cardiovascula...</b> 259:12 <b>care</b> 7:5 21:8 22:11,13 24:18 29:17 33:1 34:17 39:16 41:9 60:3 72:22 85:15 87:3,15 89:16 90:1,11 91:3 101:9 174:7 175:21 176:2,3 176:15 177:11 178:3,5,10,12 179:2 180:18 181:5,6 239:1 277:4,7 281:18 294:1 320:10 332:9,13 335:22 342:10 346:13 355:22 356:18 359:13 360:10 <b>career</b> 342:16 <b>careful</b> 64:20 <b>carefully</b> 96:21 109:7 113:10 357:18 <b>caregivers</b> 32:12 <b>Carolina</b> 5:8 9:9 26:9 250:17 <b>carried</b> 150:13
<b>Buchman's</b> 247:17 <b>building</b> 15:1 318:5 <b>built</b> 244:17 290:13 <b>bullet</b> 327:15 <b>burden</b> 34:17 90:10 <b>burdensome</b> 87:2 <b>bureau</b> 13:21 <b>burning</b> 130:15 <b>business</b> 6:8 <b>button</b> 8:15 92:10 <b>buy</b> 182:15 279:5,17	<b>C</b> <b>C</b> 6:1 271:19 <b>CA</b> 247:18 248:10 250:18 257:17 295:11 <b>cake</b> 380:22 <b>calcium</b> 230:2 <b>calculate</b> 321:19 <b>calculated</b> 57:20 252:17 <b>calculating</b> 329:22 <b>calculations</b> 195:3			

<p><b>carry</b> 364:3  <b>cars</b> 290:9  302:12  <b>carton</b> 89:13  <b>carved</b> 217:10  <b>carving</b> 261:16  <b>case</b> 48:19 64:14  68:14 69:22  70:5 75:18  125:16 127:18  133:2 158:7  162:9 185:8  238:8 246:9  271:15 310:9  344:7,8 373:8  <b>cases</b> 27:4 47:7  64:21 68:15  71:8,21 72:3  118:6 120:5  125:13 158:14  158:22 163:15  163:16  <b>Castillo</b> 4:19  326:16,16  <b>cat</b> 344:13  <b>catch</b> 283:17  <b>categories</b> 64:7  65:7 102:21  104:18 153:2  157:22 175:2  177:15 203:1  <b>categorization</b>  212:2  <b>categorize</b> 80:18  <b>category</b> 81:7  82:14 103:1,14  104:7,12,20  191:18  <b>cathartics</b>  229:13  <b>catheter</b> 32:1  <b>Caucasian</b>  144:21  <b>causality</b> 163:14  <b>causation</b> 363:7  363:8 366:20  <b>cause</b> 27:8 31:6  31:10 104:15</p>	<p>209:15,18  279:2 316:2  <b>caused</b> 105:22  <b>causes</b> 21:11  209:12  <b>causing</b> 311:1  <b>caveat</b> 106:2  <b>caveats</b> 104:12  <b>CDER</b> 10:13  <b>cell</b> 7:20 159:8  160:12,15  265:14 269:22  <b>cells</b> 169:7  235:20 269:17  <b>census</b> 31:20  <b>Center</b> 1:2 2:5,8  2:20 3:3,17,20  3:22 4:4,6,8,10  4:12,14 9:15  <b>centers</b> 133:1,5  133:6 178:8  181:7 367:4  <b>central</b> 37:3  116:2,8,9  166:9 208:9  209:19 210:4  <b>cerebral</b> 150:3  <b>certain</b> 150:14  160:7 164:10  176:10 177:1,2  178:10 240:8  276:5  <b>certainly</b> 93:19  95:17 97:11  98:13 99:1  102:7 104:22  106:2,4 111:6  112:17 115:13  122:10,13,14  124:2 127:4  130:7 200:22  201:13 216:7  217:12 222:4  233:17 237:19  245:21 246:16  249:17,19  279:19 305:6  313:11 321:16</p>	<p>331:21 337:3  348:13 373:16  382:21  <b>certified</b> 178:3,6  <b>cessation</b> 27:14  <b>cetera</b> 116:6  123:17 164:9  187:10,15  197:22 207:17  223:10 229:5  242:21 248:9  249:16 320:8  364:5,8,12  <b>chain</b> 183:7  299:3  <b>chair</b> 2:3 7:1  118:20 271:11  327:14 330:18  381:12  <b>chairman</b> 92:3  118:14 369:15  <b>Chakraborti</b>  3:21 165:22  207:10,18  208:3,19 209:4  <b>challenge</b> 257:2  <b>challenging</b> 73:4  100:14 122:12  358:3 367:9  <b>chance</b> 61:8  257:19 258:2  275:22 276:4  283:2 303:12  309:16 314:11  357:21  <b>Chang</b> 2:5 9:13  9:13 108:22  109:1,1 205:2  205:3 207:2  235:2,3 272:21  287:2 298:9  299:7,8 306:5  306:5 329:3,3  335:17,18  351:17,17  356:10,11  370:22,22  <b>change</b> 70:2</p>	<p>200:18 245:10  259:2 288:19  <b>changed</b> 195:22  222:21 331:2  <b>changes</b> 94:2  183:4,11 224:2  <b>channels</b> 36:15  <b>Chappelle</b> 7:17  <b>characteristics</b>  161:4 164:11  187:9 356:22  <b>characterize</b>  175:1 360:5  <b>characterized</b>  43:4 61:20  135:15 147:6  333:19 360:22  <b>characterizing</b>  35:17 47:18  <b>charge</b> 226:17  <b>Charles</b> 26:6  <b>Charlie</b> 5:3  269:4  <b>cheap</b> 239:5  <b>check</b> 359:20  <b>checking</b> 185:7  <b>checklist</b> 177:6  <b>chemistry</b>  116:13  <b>chest</b> 64:5 93:6  <b>chief</b> 60:18  369:4  <b>children</b> 12:19  <b>Chinese</b> 169:7  <b>choice</b> 96:8  <b>choose</b> 115:8  186:6 187:1  190:14  <b>chose</b> 119:13  189:6 198:15  <b>chosen</b> 38:14  118:6 184:5  <b>Chris</b> 119:1  <b>Christmas</b>  290:12  <b>chromosomal</b>  169:2,6  <b>chronic</b> 22:13</p>	<p>24:6 61:12,20  62:2 63:20  137:18 147:3,5  147:8 156:12  166:16 168:15  224:1 226:7  281:3 336:13  342:17 361:15  <b>chronically</b>  40:18  <b>claim</b> 146:8  <b>clarification</b>  130:22 131:7  272:12 304:20  326:8  <b>clarify</b> 101:13  125:20 216:11  274:6 284:18  294:22 325:14  330:16 361:11  362:1 366:13  366:15 367:16  374:2  <b>clarifying</b>  272:20  <b>class</b> 21:4 179:4  360:13  <b>classes</b> 309:20  <b>classification</b>  71:4  <b>classified</b> 71:5  104:14 118:4  <b>clastogenicity</b>  76:13  <b>Claudia</b> 4:7 10:3  <b>clear</b> 76:22  85:16 129:2,3  129:6 197:7  199:17 270:4  270:10,22  298:16 345:5  361:16 372:5  383:11  <b>cleared</b> 111:21  <b>clearly</b> 34:9  89:13 90:14  194:19 198:8  237:4 248:19</p>
---	---	--	---	---

270:17 333:20 334:6 336:22 345:1 <b>Cleveland</b> 3:9 4:20 9:22 26:6 <b>Clinic</b> 3:9,13 9:12,22 <b>clinical</b> 23:14,16 25:9,15 28:4 30:20 31:3 33:15 35:2,7 35:16 37:12 39:4 41:2,21 44:15,20 45:8 47:18 48:1 51:22 55:12 56:11 59:3,14 61:6,15 64:22 66:16 70:10,16 73:13 76:9,21 77:18 81:12,12 81:20 84:11 90:9 93:19 94:2,9,12 96:4 101:17 104:1 108:3 113:4 114:1 117:8 120:4 133:10 134:9,16,18 137:2,9,10 143:5 147:14 148:10 193:6 194:17 214:11 214:16 216:2 223:21 236:15 245:20 249:10 256:10 258:3 259:19,22 261:5 278:3 284:5 302:14 302:17 303:8 324:2 333:15 335:21 357:14 371:20 381:16 382:2 385:9 <b>clinically</b> 18:21 24:22 41:1 42:8,14 60:10	85:17 90:14 144:8 235:6,11 235:13 237:16 238:10 242:5 260:15 264:18 289:12 291:12 293:5 294:21 295:5 300:11 301:10,14,20 304:16 305:14 334:10,14 382:8 <b>clinician</b> 295:13 332:18 <b>clinicians</b> 34:18 122:10 273:17 312:10 <b>clinician's</b> 116:12 <b>close</b> 124:4 197:8,12 243:10 286:11 286:11 <b>closely</b> 42:9 174:1 197:13 <b>closer</b> 250:22 292:11 <b>closing</b> 340:11 <b>Clostridium</b> 106:15,20 <b>clozapine</b> 174:14 360:20 <b>Cluster</b> 231:6 <b>clustering</b> 65:20 234:19 <b>CMS-mandated</b> 33:21 <b>CNS</b> 116:19,21 117:1 208:5 209:3,5,7 <b>coded</b> 32:13 <b>coders</b> 32:9 <b>coding</b> 30:4 <b>colectomy</b> 40:16 213:21 <b>colitis</b> 2:14 235:20 <b>collaborated</b>	22:6 <b>collaborating</b> 262:3 <b>collaboration</b> 44:3 <b>collaborative</b> 367:4 <b>colleague</b> 23:19 60:14 156:10 283:1 <b>colleagues</b> 116:13 301:7 303:5 347:13 347:14 348:18 <b>collect</b> 186:15 206:1,9 311:9 <b>collected</b> 152:12 206:15,20 274:19 <b>collection</b> 31:18 75:1 120:19 181:20 318:3 <b>collectively</b> 84:14 115:11 <b>College</b> 26:16 81:19 <b>colon</b> 29:5 52:2 52:5 203:15 286:13 <b>colonic</b> 42:6 <b>colorectal</b> 34:3 50:4 <b>colostomy</b> 40:16 <b>column</b> 142:19 170:14,15 <b>combination</b> 67:18 122:17 <b>combine</b> 81:5 115:1,10 121:11 204:9 337:17 <b>combined</b> 23:3 60:5 169:22 170:8,19,20 171:4 204:7,11 204:12 326:18 326:19 350:10 <b>Combining</b>	159:20 <b>come</b> 93:15 116:13 125:7 193:16 195:15 205:11 219:5 236:15 249:14 315:2,9,14 317:11 349:1 359:3,6 373:17 378:17,19 <b>comes</b> 63:15 126:3 202:12 274:18 356:21 <b>comfortable</b> 122:16 281:12 336:7 <b>coming</b> 231:13 242:10 260:16 268:8 278:1 386:1 <b>commander</b> 369:3 <b>commend</b> 92:14 <b>comment</b> 95:4 122:2 219:9,17 226:11 227:18 274:10 281:15 286:5 294:15 297:21 305:5 307:19 323:11 327:3 330:16 349:1,20 366:13 <b>commenting</b> 295:14 <b>comments</b> 94:14 99:22 205:4 284:14 287:2 293:12 296:7 296:15 297:11 297:17 305:9 310:15 331:17 334:5 335:12 343:15 349:17 357:12,17 358:14 366:14 367:18 376:2 381:10	<b>commitment</b> 25:3 <b>committee</b> 1:7 2:2 7:3,5,12 8:4,11 10:21 11:3,5,19 12:12,15 13:15 16:1,11 20:22 61:7 68:13 71:1 77:15 81:13 92:7 118:5 120:22 121:1 130:16 133:16 183:19 210:18,20 212:13 241:18 281:16 283:19 283:20 285:22 287:11 293:12 303:22 304:3 331:3 349:17 381:8,22 382:18 383:12 384:3,8 385:11 <b>committee's</b> 11:12 19:19 <b>common</b> 21:10 27:7 31:10 51:9 52:5 79:18 80:2 89:6 102:18 111:5 159:7 219:5 221:13 249:8 288:13 <b>commonly</b> 33:16 33:20 37:19 62:5 79:12 165:4 218:10 266:5 <b>Commonwealth</b> 3:5 8:22 <b>communicate</b> 175:20 <b>community</b> 132:2 221:12 291:4 340:20 <b>comorbidity</b> 215:8 339:18
---	--	---	---	---

<b>companies</b> 300:17	24:16 91:20	279:16 353:4	327:8 328:16	61:20 62:11,22
<b>company</b> 20:12	<b>competence</b> 124:8	<b>component</b> 37:9	331:4,6 334:2	63:9 94:12
92:15 358:20	<b>competes</b> 36:17	43:22 45:17	334:17 347:10	109:18 115:5
376:20 380:1	<b>competing</b> 13:22	87:12 88:16	347:18 361:14	136:6 147:5
380:21	14:5,12	175:7,17	362:21 365:3	215:18 261:22
<b>comparable</b>	<b>competitive</b> 36:5	220:13,15	367:9,10	271:14 276:5
39:11 47:8	94:17	275:16	382:19,22,22	301:2,18 332:5
55:21 57:9	<b>complain</b> 346:13	<b>components</b>	383:21 384:7	332:20 334:6
58:2 79:17,21	<b>complains</b>	28:11 87:8	<b>concerned</b> 181:1	334:14 342:14
80:8 103:12	346:11	174:9 223:9	185:1 201:4	<b>conditions</b> 52:8
105:13 115:4	<b>complete</b> 40:17	<b>composite</b> 42:1	248:13 262:19	63:3,10 177:12
218:19	41:20 42:8	42:13 224:9,11	281:1 317:14	177:18 301:14
<b>compare</b> 33:18	41:20 42:8	<b>composition</b>	318:6,20	<b>conducted</b> 48:5
117:11 118:2	78:6 136:12	232:15	325:20 357:19	69:13 72:7
191:2 199:11	137:6 166:21	<b>compound</b> 21:4	358:5	93:1 131:18
<b>compared</b> 42:10	168:22 179:11	116:18 208:6	<b>concerning</b>	137:10,15,17
49:10 50:12	202:19 203:4	270:11	198:1 247:17	142:9 166:14
51:6,12 53:5	<b>completed</b> 35:17	<b>comprehension</b>	<b>concerns</b> 148:21	166:17 167:1
53:22 54:15	50:5 79:2	175:14	182:3 210:13	169:11 268:10
55:17 57:2,16	152:1,5,7	<b>comprehensive</b>	211:16 307:22	<b>conducting</b>
58:16 65:9	196:2 197:14	84:7	308:15 310:3,6	23:13
67:2 73:14,18	263:12	<b>comprised</b>	310:6,7,13,18	<b>confer</b> 177:19
101:7 105:2	<b>completely</b>	180:14	310:21 318:12	<b>conference</b> 30:7
114:22 143:1	199:17 276:22	<b>comprises</b> 87:8	327:22 335:14	<b>confidence</b>
145:14 146:3	375:4	<b>compromise</b>	336:4 347:8	54:22 58:6
146:14 149:17	<b>completing</b> 51:5	32:3 59:1	348:18 382:11	64:17 65:14
150:18 153:17	72:18 197:8	<b>compromising</b>	<b>conclude</b> 25:19	67:5 68:3
158:2,10 161:1	<b>completion</b>	37:3	35:14 61:16	71:10 81:3
161:12 170:5	69:18 155:15	<b>conceivable</b>	105:16	154:4 265:6
185:10 199:18	158:8	195:6	<b>concluded</b> 69:5	267:10,11
199:19 200:6	<b>complex</b> 28:14	<b>concentrating</b>	77:15	325:18 326:20
200:14,15	<b>compliance</b>	149:1	<b>concludes</b> 92:2	326:22
209:21 283:10	11:12,20 88:5	<b>concentration</b>	<b>conclusion</b> 7:14	<b>confident</b> 83:3
283:12 308:20	88:13 89:18	113:18 167:12	152:18 293:11	112:19 113:13
335:3	175:11	167:17	315:10	262:11
<b>comparing</b>	<b>complicated</b>	<b>concentrations</b>	<b>conclusions</b> 69:4	<b>confined</b> 75:22
186:11 201:21	240:6 276:11	38:20 84:1	106:4 107:7	110:7 282:5
202:5 224:4	<b>complication</b>	208:17 274:20	157:9 162:9	<b>confirm</b> 69:14
251:5,6,7	105:22	<b>concept</b> 342:8	182:21	69:17 82:1
252:2 253:8	<b>complications</b>	<b>concern</b> 64:3	<b>concomitant</b>	<b>confirmation</b>
<b>comparison</b>	30:15,17 31:7	66:10 117:17	75:16 94:21	45:8
34:5 64:15	32:1 41:12	118:11 184:10	193:12	<b>confirmatory</b>
68:16 147:1,19	51:20 53:8	201:8 203:16	<b>concordant</b>	165:6
204:3	58:12 102:1,3	209:2 210:4,6	302:4	<b>confirmed</b> 75:7
<b>comparisons</b>	102:19 104:19	247:6 307:8	<b>concur</b> 301:6	228:14
124:6,11 204:5	106:12 116:7	312:6 313:3,4	<b>condition</b> 21:7	<b>conflict</b> 10:17,20
<b>compelling</b>	127:9 135:18	314:21 316:7	21:14 26:20	11:9,13,20
	217:1,10 272:1	322:3 325:8	34:22 37:10	12:6 13:16

14:8	70:12 87:10	3:15	172:18 268:4	352:12 369:22
<b>conflicts</b> 12:3,11	124:8 152:5	<b>consulting</b> 13:1	<b>control</b> 169:21	384:16
12:17	178:20,21	14:4	170:6,21 171:7	<b>correct</b> 104:5
<b>confounded</b>	285:18 360:8	<b>consumer</b> 15:12	182:16 183:6	123:13 124:13
49:19 68:10	382:1	<b>consumes</b> 31:12	303:18 341:21	127:19 128:5
<b>confounding</b>	<b>considering</b>	<b>consumption</b>	359:8 367:6	132:10 188:12
43:9 230:10	283:8	59:5 97:5	<b>Cont'd</b> 3:1,2 4:1	218:11 248:1,2
<b>confused</b> 369:17	<b>considers</b>	<b>contact</b> 7:16	5:1,2	248:17,18
<b>congestive</b> 150:5	269:11	151:6 205:9	<b>convene</b> 268:21	263:1,2,14
207:16	<b>consist</b> 64:7	<b>contacted</b> 83:7	<b>convenience</b>	292:18,21
<b>Congress</b> 11:22	<b>consisted</b> 39:19	<b>contain</b> 93:18	7:15	326:5,14 370:7
12:7	119:20	248:3	<b>convening</b> 11:2	<b>corrected</b> 359:2
<b>conjunction</b>	<b>consistency</b> 71:2	<b>contained</b>	<b>conversation</b>	<b>corrective</b> 88:10
264:11	114:1	224:11,14	322:7	<b>correctly</b> 114:10
<b>Conor</b> 4:19 26:5	<b>consistent</b> 23:4	<b>content</b> 172:22	<b>conversations</b>	247:21 311:15
127:17 133:2	23:10 39:5,11	179:17	7:6	325:21
238:8 246:9	39:18 43:12	<b>contents</b> 27:16	<b>converted</b> 55:6	<b>correlated</b> 31:21
<b>conscious</b> 168:1	50:2 51:22	<b>context</b> 49:18	<b>convinced</b> 261:1	<b>correlation</b>
<b>consecutive</b> 89:4	52:7 54:20	218:1 226:6	317:3 360:6	101:21
<b>consensus</b> 30:7	59:6 82:11	295:1,2 300:1	<b>convincing</b>	<b>correspond</b>
384:2 385:10	95:19 123:18	318:19 343:1	271:1	57:19
<b>consent</b> 174:6	124:18 130:4	357:16 360:22	<b>convincingly</b>	<b>corresponding</b>
177:13 312:16	217:6 258:13	<b>continuation</b>	222:3	38:10 56:11
355:17 358:3	278:2,7	197:6	<b>cooperation</b> 8:2	59:16,21
363:22,22	<b>consistently</b>	<b>continue</b> 72:19	<b>coordinated</b>	<b>corresponds</b>
364:3,11	33:13 34:14	222:11	27:14	58:18 237:7
365:17,22	142:21 152:14	<b>continued</b> 37:21	<b>coordination</b>	<b>corticosteroids</b>
<b>consequence</b>	246:3,4	38:5 154:13	33:3	313:7,9,12
362:22	<b>consists</b> 78:15	275:20	<b>Copies</b> 14:20	319:2
<b>conservative</b>	<b>constant</b> 155:7	<b>continuing</b>	<b>copy</b> 15:1	<b>Cosmetic</b> 11:16
73:13	<b>constipation</b>	176:4	<b>core</b> 97:13	<b>cost</b> 303:8,10
<b>consider</b> 119:14	19:7 61:21	<b>continuous</b>	124:21 231:5	312:10 335:19
144:6 185:22	224:1 336:13	272:16	241:18 254:22	358:17 361:10
236:19 248:22	<b>constituency</b>	<b>continuum</b>	<b>CORKERY-D...</b>	377:15
249:1 264:13	117:20	264:10 265:4	2:17 9:8	<b>costs</b> 32:4,16
272:2 284:9	<b>constitute</b> 71:8	<b>contracts</b> 13:2	107:11,12	342:10
287:12 293:3	<b>constituted</b>	87:14	226:10,11	<b>cost-benefit</b>
304:15 381:19	117:21 119:3	<b>contraindicated</b>	227:6 297:10	272:3
382:6	120:22	89:3	297:12,16	<b>cost-effective</b>
<b>considerable</b>	<b>construct</b>	<b>contraindicati...</b>	306:8 329:19	235:16 297:3
28:10	244:16	379:3,11	338:10,11	<b>cost-effectiven...</b>
<b>consideration</b>	<b>consultant</b> 5:5	<b>contrast</b> 63:8	351:16 354:18	342:2
102:9 115:5	9:10 259:10	160:11 240:22	354:19 371:2	<b>count</b> 174:18
130:2 268:16	<b>consultants</b> 11:7	<b>contribute</b> 28:22	377:8,14,20	<b>counted</b> 125:15
303:20 375:6	11:19 12:14	122:18 269:14	<b>Corporation</b> 5:5	191:16,21
<b>considerations</b>	13:15 15:16	<b>contributed</b>	5:6,15,16 13:8	192:2,5 248:14
86:1	264:12	225:1	20:15 368:16	<b>countervailing</b>
<b>considered</b> 42:7	<b>Consultation</b>	<b>contributing</b>	<b>Corporation's</b>	321:2

<b>countries</b> 218:15 218:18 231:19 233:10,17	208:10 325:19 <b>CS-7</b> 131:8 <b>Cullen</b> 2:18 8:19 8:19 14:9,10 228:16,17,17 296:8,9,18 306:13,13 329:16,16 346:9,10 351:13,13 353:6,7 365:4 371:6,6	242:3 243:9 250:19 252:4,7 253:5 272:17 <b>culp</b> 301:11 <b>cut</b> 258:12 266:15,15 <b>cuts</b> 266:16 <b>CV</b> 66:1 67:18 68:21 80:21 82:1 150:20 154:5,21 155:2 155:6,9,20 156:1,13 <b>CVD</b> 191:14 <b>cycle</b> 136:12 137:8 140:20 141:2 196:7,14 <b>cyclical</b> 242:3	31:18 32:6,9 32:17 45:20 52:12 54:15 60:20 61:8 63:15 67:20 68:12 74:16 76:4,22 77:16 80:17 82:7 83:3,17 85:16 86:7 90:12 92:16 101:9,20 106:8 107:5 108:12,18 110:8 112:17 120:19 121:10 122:13 123:19 129:6 132:6 133:4,8,18 134:5 140:22 143:19 144:18 145:22 152:15 184:1,16,17 185:5,11 186:4 186:15 188:6 189:8,9 190:6 190:9 192:14 193:1 194:10 198:2,3,16,18 198:19,22 199:4 201:4 203:16,20 204:14 205:13 205:18 206:1 208:16 212:6 214:14 216:4,4 216:6 217:12 217:21 218:8 221:8,17 222:3 222:13 223:4,8 223:15,17 227:1 230:1,5 239:18 241:1 241:15 250:11 255:7,11 258:20,21 259:13 260:11 261:19 262:6 262:10 263:15	270:21 271:17 274:18 280:12 282:2,3,10 294:18 295:5 297:8 299:4,21 307:7 313:5,6 313:15 315:11 318:3 319:14 325:6,20 327:21 336:5 341:8,12 343:8 345:5 348:14 350:8,17 362:4 364:18 371:18 373:16,19 376:5 377:2 380:11 382:10 383:3 385:6 <b>database</b> 68:18 71:18 78:10,14 78:17 82:9,9 82:12,17 83:5 84:12 95:9 110:14 144:15 214:19 223:16 230:6 256:3,19 274:3 281:19 323:5 366:8 368:6 <b>databases</b> 87:16 257:4 322:22 <b>data's</b> 198:10 298:15 <b>date</b> 137:8 293:7 <b>David</b> 5:6 60:14 60:18 213:15 268:12 281:11 <b>day</b> 38:4 39:21 39:22 40:2,2 43:14,15 44:14 53:4,4 55:3 57:15,21 58:1 59:15,19,20 62:14 100:22 101:18 107:19 125:12 138:9 138:11 142:18 143:12 144:1
<b>couple</b> 92:17 102:9 258:18 261:10 262:17 276:15 322:14 336:12 349:2 365:10	<b>cultural</b> 49:13 <b>cumulative</b> 280:11,14,16 281:9 313:10 313:11,15,20 316:14,17 319:1,4 350:17 383:1	<b>D</b>		
<b>course</b> 17:17 94:11 117:18 120:4 181:12 223:1 241:15 251:9,13 270:12 282:21 289:2 292:4 317:9 322:3 326:2 376:7	<b>curious</b> 184:4 198:15	<b>D</b> 6:1		
<b>covariate</b> 97:1	<b>current</b> 32:21 34:12 39:18 95:9 147:10 167:12 181:1 239:9	<b>daily</b> 62:18,20 63:4,22 76:17 88:6 164:20 180:9 288:13 332:9		
<b>coverage</b> 130:9	<b>currently</b> 16:22 18:2 21:12 33:20 93:18 135:20 274:3 307:7 327:21 365:12 371:17 382:10 385:6	<b>Dana-Farber</b> 5:3 26:7 269:6		
<b>covered</b> 11:14 110:9	<b>curve</b> 53:1 67:16 96:11,18 112:20 113:5 237:6,6,11,12 237:17 242:14 242:15 251:21 252:1,1 316:17	<b>danger</b> 364:4,10		
<b>Cox</b> 46:19 47:6	<b>curves</b> 47:3,11 47:13 52:10,16 53:8 56:9 96:13 132:14 197:21 236:17 240:3 241:19 241:21,22	<b>dangerous</b> 365:21		
<b>co-investigator</b> 14:11		<b>Dannis</b> 4:3 134:19 148:5 148:12,13 180:3 187:8 190:22 191:19 194:15 195:13 197:20 201:20 202:14 205:7 206:10 207:5 223:20 262:20 263:8 272:22 326:10		
<b>CP-11</b> 117:12		<b>data</b> 19:11,21 21:14 22:20 23:20,22 24:1 24:4,7,8,15 25:14,15 30:7		
<b>CP-9</b> 117:12				
<b>CRADAs</b> 13:2				
<b>cramping</b> 62:12				
<b>creating</b> 310:17				
<b>criteria</b> 34:15 40:3 64:4 74:22 118:7 120:2 121:5 246:1 269:10 337:21 360:15 379:15,20 380:15				
<b>critical</b> 15:14 288:12				
<b>Crohn's</b> 314:4				
<b>Crohn's</b> 2:14				
<b>cross</b> 116:15				

155:14,14	275:6,9 276:17	260:19 262:12	246:7,9,9	<b>denominator</b>
168:16,18	279:2,10,10	299:20 302:10	273:2	285:15 334:18
169:13,15	281:2,4,6,7	342:11 356:9	<b>Delaney's</b>	375:18
170:7 188:11	285:12,17	384:19	243:22	<b>denominators</b>
189:12 190:14	287:15,16,16	<b>decisions</b> 49:14	<b>delay</b> 217:4	224:2
190:14 235:10	287:17,18	174:4 312:9,11	<b>delayed</b> 21:11	<b>denominator's</b>
237:7,15 238:9	288:4 291:17	<b>decrease</b> 34:21	44:11 59:18	199:15
238:14,19	295:21 307:10	126:1 266:7,12	135:19 143:7	<b>deny</b> 383:4
239:2,4,6,14	311:19 313:8	267:9	216:14,22	<b>Department</b> 2:9
240:1,4 242:8	316:16 317:22	<b>decreased</b> 147:6	<b>delete</b> 369:19	3:8,13,17
242:8 255:1	318:2 328:2	275:1 345:7	<b>deleterious</b> 33:8	250:17
260:4 275:10	368:4 372:17	<b>decreases</b>	77:1	<b>departure</b> 43:8
275:11 287:10	377:10,13	271:18	<b>deliberations</b>	<b>depend</b> 323:1
288:2,2,8	382:13	<b>deemed</b> 224:16	14:16	<b>depending</b>
289:17 292:11	<b>day's</b> 20:10	<b>define</b> 81:21	<b>delivered</b> 176:1	173:13 372:20
295:17 296:12	<b>DBT</b> 34:2	197:11 354:4	270:9	<b>depends</b> 98:2
297:1,1 301:15	<b>DCR</b> 117:16	359:12	<b>delivery</b> 303:10	246:19 285:14
301:15,17,17	<b>DCRI</b> 81:18	<b>defined</b> 18:7	<b>delta</b> 36:12	299:3 368:4
301:19 337:15	<b>deal</b> 194:16	27:13 43:6	<b>delta-receptors</b>	<b>deputy</b> 10:10
338:13,14	337:20	44:7 46:7,10	259:15	<b>derived</b> 47:2,6
344:11 371:16	<b>dealing</b> 244:17	74:22 139:12	<b>DeLuca</b> 9:8	<b>describe</b> 46:21
<b>days</b> 30:9 34:8	271:13 276:11	150:2 152:13	306:8 329:19	207:11 337:6
38:1,5 40:19	278:19 334:13	255:6	338:11 351:16	363:13
44:9,13 49:9	350:11,13	<b>defining</b> 43:20	354:20 371:2	<b>described</b> 14:17
52:19 53:6	<b>deals</b> 332:19	<b>definitely</b> 189:3	377:7	17:9 47:20
54:14 56:6	<b>Deanne</b> 5:4	275:15 299:16	<b>demanded</b> 197:1	88:20 187:9
59:15 66:11	259:9	341:22 354:7	<b>demographic</b>	294:1
83:17 84:3	<b>Dear</b> 176:2	<b>definition</b> 44:2	144:17 161:4	<b>describes</b> 89:6
89:5,9 91:1	<b>death</b> 74:7 80:8	44:17 120:2	164:10	151:1 162:20
100:10,14,17	146:20 149:18	181:5 193:22	<b>demographics</b>	<b>Desegter</b> 210:5
101:11 103:8	149:19 150:8	246:4 248:21	51:15 155:20	210:10,11
109:14 131:11	154:16 159:16	255:5 286:9	156:1 164:16	<b>design</b> 35:13
132:7,8,11	161:21 224:15	373:3	<b>demonstrate</b>	37:13 157:8
142:6,15,22	264:19 265:3	<b>definitions</b>	25:9 38:19	236:20 363:16
143:16,17	265:19 267:4	64:13 68:10,14	58:5 60:10	380:15
147:10,22	<b>deaths</b> 73:15,17	102:15 359:15	73:22 90:14	<b>Designated</b> 4:13
151:7,8,13	119:14 120:1	359:18 372:9	95:16 97:9	<b>designation</b>
155:1,5,10	154:15 157:12	<b>definitive</b> 76:15	100:11 270:10	136:3
158:8 188:10	159:17,19	106:4	<b>demonstrated</b>	<b>designed</b> 9:17
188:17 189:14	160:10,14	<b>degree</b> 198:7	36:13 39:4	18:2 45:10
189:16,20,22	<b>debilitating</b>	314:21	55:18 57:3	73:8 102:11
190:8 204:18	62:22	<b>Delaney</b> 4:19	76:10 102:5	105:19 152:19
227:5 240:15	<b>decade</b> 28:9	26:5 127:2,14	137:20 143:19	173:5 196:19
251:12 254:16	238:12 257:20	127:16,18	209:9 210:2	331:1 363:17
254:19 255:8	258:4 287:9	132:19 133:2,2	229:20 335:8	379:18
260:7,11,12	<b>decide</b> 261:2	236:15 238:6,8	383:22	<b>designs</b> 152:8
271:5 272:18	<b>decided</b> 138:1	238:8 239:15	<b>demonstrates</b>	<b>desirable</b> 352:16
273:13 274:5	<b>decision</b> 182:14	244:7 245:20	346:20	<b>desired</b> 72:21

174:11 175:15	<b>devoid</b> 220:7	260:12 262:21	336:16 368:12	38:10 41:4
<b>Despite</b> 30:1	<b>diabetes</b> 149:10	272:17 284:10	368:12 373:12	43:5,7,13
<b>detail</b> 117:19	214:10,12,15	289:11 290:18	374:18	44:12,13,15
119:12 183:1	214:19 215:3,8	290:22 295:12	<b>differentiate</b>	49:5,7,14
372:12	226:13,16	295:17,21	80:5 194:2	55:11 56:7,15
<b>detailed</b> 73:6,19	<b>diabetic</b> 187:15	308:22 309:19	<b>differentiation</b>	57:14,21 59:18
113:3 120:14	<b>diagnose</b> 30:10	318:22 337:21	303:15	59:20 91:1
179:15	<b>diagnosis</b> 73:10	341:17 342:20	<b>differently</b>	112:22 114:16
<b>detailing</b> 88:7	105:6 265:21	349:4,8,9,10	118:4 205:1	114:17 131:21
176:10	<b>diarrhea</b> 62:12	381:20 382:1	250:15 305:10	139:11 141:18
<b>details</b> 7:13	<b>died</b> 159:21	<b>differences</b>	<b>difficile</b> 106:15	142:5 143:4,6
117:15 118:9	<b>Diego</b> 10:2 92:13	47:12,15 48:12	106:20	143:7 151:9,18
<b>detect</b> 83:2	<b>diet</b> 39:22 128:7	49:13,15 50:13	<b>difficult</b> 80:5	152:3 188:8
310:2	246:13 247:4	56:1,4 57:7,9	86:15 105:5	193:8 195:2
<b>determinant</b>	289:20	57:19 59:13	127:10 139:6	216:14,22
49:5	<b>dietary</b> 33:5	71:3 98:17	159:3 160:2	217:5 235:10
<b>determine</b> 41:16	<b>diff</b> 271:19	102:11 107:4,8	185:17 189:18	239:21 240:10
80:19 95:10,15	<b>differ</b> 81:22	140:9 141:11	190:2 203:3	241:19,22
181:21 192:15	211:22 222:19	142:18 150:16	264:3 279:20	242:4 243:19
294:8	<b>differed</b> 46:1	154:8,13,18	327:5,7 337:6	244:5,10,11
<b>determined</b>	<b>difference</b> 47:9	155:19,22	361:17 363:21	246:1,14,17
11:18 12:3	53:10,13,14	162:1 188:20	365:17	247:11 254:10
18:10 163:15	54:10,12 56:17	199:1,2,16	<b>difficulties</b>	254:20 278:8
235:14,17	56:18,19 58:17	200:8 234:20	198:4	290:9 293:7,8
<b>determines</b>	68:20 69:1	250:6 252:10	<b>digest</b> 355:20	299:2,12
116:2,8	72:2 98:1	267:7 284:21	<b>dilemma</b> 244:3	300:12,15
<b>determining</b>	106:19 112:14	<b>different</b> 15:8	<b>diminished</b>	301:1 302:10
293:18	116:9 121:7	17:18,19 23:17	71:14	382:3
<b>develop</b> 27:11	122:9 126:5	85:22 109:22	<b>dinner</b> 289:1	<b>discharged</b> 69:7
34:15 214:12	142:10 144:3	110:12 140:11	<b>direct</b> 28:18	77:17 106:9
261:13 270:14	147:15 148:1	143:4,5 150:15	264:5	138:10 139:14
<b>developed</b> 44:3	150:10 162:14	156:18 175:1	<b>directed</b> 89:16	242:11 255:1
<b>developing</b>	162:16 169:20	176:1 184:14	89:22 363:10	<b>discharge-rela...</b>
17:11 22:5	170:5 183:21	189:6 190:20	<b>direction</b> 124:12	49:17
28:12	184:7 185:4	193:6 194:5	320:13 321:9	<b>discharging</b>
<b>development</b>	188:7,11	199:3,15	<b>directly</b> 31:21	247:7
17:16,18 19:6	189:11,12	202:20,22	37:8 108:3	<b>discomfort</b> 28:8
19:13 22:7	190:13,21	203:1,7 204:5	<b>director</b> 10:11	31:4
25:4,13 28:22	192:19 193:5	204:10,18	10:13 35:5	<b>discontinuation</b>
32:8 35:2 37:6	200:2,9 202:11	211:20 212:4	61:5	50:6
37:12 40:21	225:10,17	224:10 233:15	<b>direct-to-cons...</b>	<b>discontinuatio...</b>
48:2 61:6	237:14 240:14	239:1 241:3	176:9	51:9 145:21
70:11 90:13	241:11,13	243:4 247:19	<b>disagree</b> 317:19	146:1,20
119:10 229:22	242:20 243:15	251:4,8 257:19	<b>disappointed</b>	<b>discontinued</b>
261:6 275:8	248:16 251:19	276:22 308:16	323:5 360:2	79:3,6 151:20
359:4	252:3,5,12,14	308:17,19	<b>discharge</b> 18:6,8	<b>discount</b> 249:6
<b>developmental</b>	252:14,20	315:14 317:20	21:11 22:4	<b>discounted</b>
167:4	255:15 258:4	318:13 336:6	34:7 37:22	383:10

<b>discounting</b> 249:17	69:6 73:2,11 74:4 77:14	87:2,12 166:13 175:4 177:16	<b>dosage</b> 180:9	209:8 210:15
<b>discover</b> 312:22	110:16,22	177:22 208:7	<b>dose</b> 23:6,9 24:3	220:16 221:15
<b>discovered</b> 158:7 202:14	161:5 190:3,3 190:11 228:15	231:3 259:14 267:19	37:16 38:6,16	222:6 280:11
<b>discrepancies</b> 99:13	231:11 234:4 264:19 345:20	<b>divergence</b> 53:9	39:1,13 46:11	307:10 328:2
<b>discrepancy</b> 161:20	<b>diseases</b> 3:11 9:2	<b>diversion</b> 183:9	62:19 63:4,11	375:9 382:13
<b>discrete</b> 363:20	214:1	<b>diverted</b> 363:5	78:20 83:6,17	383:3
<b>discretion</b> 40:12 93:2 94:10	<b>dismiss</b> 309:2,5	<b>diverticular</b> 52:6	84:4 86:1,12	<b>dose-ranging</b> 38:13
<b>discuss</b> 17:5 19:14 21:2	<b>dismissing</b> 250:8 327:7	<b>divide</b> 86:15	94:20,22 95:7	<b>dose-response</b> 112:20 113:5
25:17 35:2	<b>disorder</b> 226:7	<b>divided</b> 153:1,19 157:20 233:16	95:12 96:22	<b>dosing</b> 37:21 38:20 129:18
39:9 46:3	<b>disorders</b> 214:13	<b>Division</b> 2:3,11 2:19 3:22 4:3,5	97:6 100:17	130:12 147:16
79:10 99:2	<b>disparity</b> 354:10	4:9 10:9,11	112:5,10	272:5
156:11 157:10	<b>dispense</b> 178:7 180:21 181:10	134:3,8	113:13,14,21	<b>double-blind</b> 63:18 137:11
167:8 169:18	211:9	<b>dizziness</b> 164:8	114:2,3,11,13	<b>doubling</b> 32:16
194:8 214:6	<b>dispensed</b> 90:6 178:9	<b>doctor</b> 107:15	114:18,19	<b>Douglas</b> 3:14 8:17
219:13 278:15	<b>dispensing</b> 176:19 177:22	<b>doctors</b> 311:9	115:8,8,12	<b>DOW</b> 43:7 56:17,22 139:8
287:6 293:3,15	178:4,13	<b>document</b> 14:18 35:22 47:4	117:4 126:16	139:13 142:6,6
<b>discussed</b> 6:15 64:7 93:9	<b>Disposition</b> 78:22	49:21 73:20	127:11 129:10	142:14,20,22
197:5 220:9	<b>dissimilar</b> 276:1	128:17 191:17	129:12,17	143:5 188:8
242:2 271:20	<b>distance</b> 252:6 253:1	261:12 309:12	138:6 147:17	193:8 295:6
275:14 331:8	<b>distances</b> 253:4	<b>documentation</b> 80:13 118:8	164:20 168:4	296:11 302:2
334:7	<b>distended</b> 346:19	120:6,7 178:14	169:21 170:6	302:16
<b>discussing</b> 7:13 113:16 148:14	<b>distension</b> 28:7 31:5 79:16	<b>documented</b> 30:3 32:8	170:16 171:1,7	<b>downside</b> 380:4
149:2 222:12	<b>distention</b> 346:18	<b>documents</b> 81:18 179:14	171:12 180:10	<b>downsides</b> 312:17
355:11	<b>distinct</b> 32:6 62:1	<b>dofetilide</b> 182:11	183:22 184:3,4	<b>downstairs</b> 210:18
<b>discussion</b> 6:19 13:5 17:13	<b>distinguish</b> 181:6	<b>dog</b> 167:13 168:17 289:3	184:11,11,20	<b>Dr</b> 6:3,5 8:3,14 8:17,19,21 9:3
20:7,10 22:17	<b>distribute</b> 87:13 87:15 178:17	<b>dogs</b> 168:1	184:21 186:3	9:5,11,13,14
45:18 61:14	<b>distributed</b> 145:6 150:21	<b>doing</b> 97:3 185:15 202:15	186:10,18	9:21 10:1,8,10
78:7 92:6	207:19 208:4,8	205:14 224:9	272:4,7 273:13	10:12,14,15
144:8 184:20	208:12 366:22	237:18 242:17	274:6,11,16,17	13:20 14:1,3,6
194:11 211:10	<b>distribution</b> 72:3 86:20,22	243:18 265:16	275:4,19,21	14:9,10 16:4,4
211:20 222:17		294:10 327:8	279:9,18	16:10,10 19:3
251:15 286:22		338:16 339:17	280:14,16	20:11,14,21
342:9 374:9		357:20 375:6	281:4,9 313:11	23:19 25:5,10
<b>discussions</b> 12:13 15:16		376:6 378:12	313:15,16,18	25:12,14,16,19
197:4,17		<b>dollar-saving</b> 327:10	313:20 322:2	26:12,13,14
322:12			341:11 383:2	34:6 35:1,4
<b>disease</b> 52:7 65:19 68:10			<b>doses</b> 23:1 37:15	41:6 60:14,17
			38:12 39:11	60:22 61:4,5
			40:19 62:4,10	78:6,8,9 83:19
			62:12 72:15	
			76:16 79:8	
			86:15 89:10	
			96:1,2 99:14	
			108:16 114:10	
			129:11 138:8	
			138:12 140:11	
			166:5 169:12	
			169:14 184:14	

84:12 90:17	193:11,18	233:5,20,20,22	286:20,21	327:18 328:8,9
92:5,11,12	194:6,13,13,14	234:9,10,12	287:2 288:20	328:11,14,20
93:13,13,15	194:15 195:13	235:2,2,3	288:20,21	328:21 329:1,2
94:4,5,13,13	195:16,16,17	236:9,14,15	289:13,13	329:3,4,5,7,11
94:15,15,16	195:18,20	237:9 238:6,8	290:1,2,2,3,4,5	329:12,13,14
95:5 96:20	196:6,21 197:3	239:4,15	290:6 291:2,2	329:15,16,17
97:2,7,10,20	197:18,18,19	240:22 241:16	291:3 292:4,8	329:18,21
97:21,22 98:2	197:20 198:21	243:22 244:14	292:10,12,15	330:3,14
98:4,11 99:4,4	199:5 201:20	244:14,15	292:17,19,21	331:17,19
99:5 100:2	202:4,14	245:18,20	293:13,14	332:17,17,18
101:14 102:6	203:11,11,12	246:7,9,10	294:1,16,16,17	333:4,4,5,13
103:22 104:2,5	204:1,1,11	247:14,14,15	295:9,9 296:6	333:13 334:4,5
104:6,8,9,10	205:2,2,3,4,7	247:17 248:2,5	296:6,8,9,14	335:1,2,13,17
106:6 107:1,9	206:10 207:1,1	248:8,10,11,13	296:14,16,17	335:17,18
107:9,12,22	207:2,5,6,6,7,8	248:18,19	296:18 297:10	336:20,20,21
108:2,6,22,22	207:9,10 208:1	249:11,14	297:14,19,19	338:10 341:4,4
109:1 110:4,8	208:16 209:1	250:13,16	297:20,21	341:5,7 342:6
111:7,13,16	210:8,16 211:3	253:10,21,22	298:9,9,10,11	342:6,7,13
112:3,3,4	211:18 212:11	254:1,2,8	298:12,15	343:13,13
113:2,2,9	212:21 213:1	255:18,18,19	299:7,7,8,9,17	344:17,17,18
115:3,16,16,17	213:13,15,16	256:5,5,7,8	300:2 301:8,12	345:17 346:9,9
116:10,20,22	213:19 214:7,7	257:14,14,15	303:3,3,4,6,11	346:10 348:1,5
117:5 118:12	214:8,17,17,20	257:16,16	303:11,13,14	348:8,22
118:13,16,16	215:21 216:6,9	258:5,17,17,18	303:16,21	349:19,20
121:2,2,3	216:9,10,16,20	259:7,8,9,17	304:6,19,21,22	350:4,6,19
122:3,7,8	217:2,6,8,11	259:17,18	305:4,11,13,19	351:11,12,13
123:3,5,6,8,9	217:14,14,18	261:5 262:16	305:20,21,22	351:14,15,17
123:11,13,14	218:6,9 219:4	262:16,17,20	306:2,4,5,6,9	351:18,19,20
125:6,9,21,22	219:7,8,11,12	263:7,8,10,15	306:10,12,13	351:21 352:2,3
126:4,7 127:1	219:22 220:1,5	263:19 264:4	306:14,15,19	352:4,6,9,17
127:2,14,16,17	220:18,18,19	268:12 269:4	306:21,22	352:18 353:6,6
128:13,16	220:20 221:7	271:11 272:10	307:4,4,20	353:7,7,10,10
129:8,19	221:19 222:2,9	272:14,19,21	308:13,13	353:11,12,16
130:13,14,19	222:9,10	272:22 274:8,9	310:4,4,5,20	353:16,20,20
130:20 132:4	223:11,12,13	274:14 275:7	310:20,21	353:21 354:6,6
132:19 133:2	223:14,20	275:12,13	312:15 313:4	354:7,18
133:13,22	226:10,12,18	276:6 277:2,9	314:19,20	355:13,13,14
134:2,6,19	226:20 227:8	277:11,13	315:12,12,13	356:10,10,11
148:5,12,13	227:14,17,20	279:1 280:10	315:20 316:1	357:7,7,8
180:3 183:17	227:20,21	280:14 281:11	316:14 317:16	358:19 360:7
183:20 184:8	228:1,6,7,16	281:17,18,22	317:16,17	361:11 362:2,3
186:9,13 187:6	228:16,17	282:1,12,15,20	318:1,15,15,16	364:15,15,16
187:6,7,8,20	229:2,19 230:5	282:22 283:1,6	322:5,5,6,7	364:17 365:4,9
187:22 188:2,3	230:8,8,9,14	283:14,16	323:10,10,15	365:9,10,18
188:4 189:3	230:17,20,22	284:16,17,22	324:4,7,8	366:12,12,14
190:17,17,22	231:2,20 232:1	285:3,8,20,20	325:10,11,13	366:14 367:12
191:19 192:8,8	232:4,7,12,14	285:21 286:6	326:6,8,10,13	367:12,13,14
192:9,17	232:17,22	286:18,18,19	327:2,2,11,13	367:14,15,22

368:10,10,21	178:9,11	385:2,19	119:10 147:4	<b>eats</b> 289:1
369:1,3,13,14	187:14 188:13	<b>drugs</b> 1:6 8:4	148:19 205:20	380:22
369:15,18	192:13,15	10:21 11:3	<b>D.P.M</b> 5:14	<b>ECG</b> 80:13
370:7,8,15,16	201:12,16	16:22 34:11		168:4
370:17,18,20	206:3,4 208:8	144:10 187:12	<b>E</b>	<b>echo</b> 334:4
370:21,22	208:18,22	187:14,15,18	<b>E</b> 6:1,1 211:1,1	335:12 344:18
371:1,3,4,5,6,7	213:4,7,11	193:12 317:2	<b>earlier</b> 22:2,3	<b>economic</b>
371:8,11,15,22	217:20 219:2	323:20 349:3	43:21 47:20	331:21 332:1
372:1,22 373:2	221:2,13 227:9	363:1,21 364:2	53:3 54:14	332:15 348:15
373:22,22	227:15 229:1	364:4,9,13	55:9 84:12	<b>educate</b> 174:6
374:1,6,17,17	245:10 249:2	373:5	106:10 140:6	<b>education</b> 26:18
375:3,4,22,22	258:22 261:13	<b>drug's</b> 380:4	141:9,22	174:5 175:2,19
376:1 377:5,5	262:22 263:6	<b>due</b> 15:13 49:15	142:15 183:22	175:22 176:5
377:9,12,17,22	264:2 268:17	51:10 79:6	218:22 219:10	180:17
377:22 378:1	269:9 270:6	99:10,19 124:5	235:10 237:21	<b>educational</b>
378:10,10,17	271:6,7,22	137:8 145:16	237:22 238:2	89:15 175:17
378:22 379:8,8	273:13 275:2	145:21 146:1,5	239:11 240:11	<b>effect</b> 29:5 39:5
379:9 380:18	277:6 278:10	146:20 155:14	244:9,10 247:4	42:12 46:18,22
380:18 381:5	279:2,7 280:6	<b>duke</b> 3:3 4:17	253:19 254:6	54:19 55:20
<b>draw</b> 106:3	287:12,13,21	5:9 9:14 26:3	267:17,18	62:8 63:19
107:6	288:18 293:19	26:10 81:12	269:16 271:18	72:11 76:16
<b>drawback</b>	298:6 303:2	82:3 94:15	278:8 279:1	77:17 95:2,8
367:16	308:10 310:11	117:8 220:19	281:16 291:11	96:17 97:17,19
<b>drawn</b> 157:9	310:16 311:21	247:15 256:9	301:3 334:7	99:12,15
162:9	312:14 315:2	348:3 350:8	<b>early</b> 33:4,4,6	100:11 102:17
<b>driven</b> 65:11	316:4,5 317:15	<b>dumb</b> 285:17	39:19,21,22	109:3 116:5,8
67:22 70:4	321:3 322:17	<b>dunk</b> 343:16,18	44:14 55:13	123:1 126:19
161:13 260:21	322:19,22	<b>duodenum</b>	90:18 126:11	128:20 129:2,9
<b>driver</b> 41:4	327:9 333:20	126:15 128:2	127:20 142:18	129:14 167:14
55:10	334:7,15 335:3	<b>duplicated</b>	184:13 188:21	167:21 168:2,9
<b>driving</b> 342:11	336:9,18	321:6	189:19 190:1	168:14 172:14
<b>dropping</b> 121:7	337:12 340:2	<b>duration</b> 37:6	242:11 243:6	188:13 192:15
<b>drops</b> 155:13	342:10 344:4	52:2 58:13	245:15 246:14	195:9 205:6
<b>Drs</b> 13:18 244:7	345:10 347:11	62:3 66:17,19	253:16 288:6	207:14 209:15
273:2	348:15,21	67:11 147:20	289:21 367:17	209:18,20,21
<b>drug</b> 1:1,2 3:18	349:5,22	156:2,22	381:6	215:11 216:2
3:20,20,22 4:2	352:21 354:10	163:22 167:15	<b>easier</b> 303:19	217:9 218:18
4:4,6,8,10,12	356:4 358:16	204:13,17	363:20	229:16 235:5
4:14 11:1,16	359:4 360:4,15	205:5	<b>easiest</b> 331:22	236:2 240:20
13:7 19:17	360:16 362:10	<b>DVDs</b> 176:8	<b>easily</b> 332:2	249:22 250:1
20:1 38:6	362:14 363:1	<b>DVT</b> 278:5	359:1	258:1 262:8
46:11 66:12,19	363:12 365:6	<b>DVT-PE</b> 102:22	<b>Eastern</b> 230:18	263:5,6 275:21
70:22 74:8	365:21 366:1	<b>dying</b> 271:15	231:14,17,22	275:22 294:11
75:7 89:1	368:1,4 372:18	323:22 342:17	232:8,19	313:12 316:14
93:11 100:18	372:21 374:20	<b>dysfunction</b>	<b>easy</b> 372:1	316:17,18
102:2 121:6,18	377:13,15	19:15 22:14	<b>eat</b> 237:22	319:4 334:9
128:13,20	379:2,11	61:11,19 109:4	<b>eating</b> 289:20	349:5 353:8
138:12 144:10	380:20 383:10	109:10 110:1	332:5	362:16 383:13

<b>effective</b> 21:15 27:15 29:21 34:14 58:20 179:1 186:10 188:15 239:3 293:20 335:20 360:10 361:4 381:2	139:16 140:22 143:18,19 144:3,6 146:8 183:21 184:2,6 188:6 189:4 235:3,4 236:11 247:22 278:2 284:5 293:4,18 295:1 303:1 304:15 305:14 306:16 318:14 334:8 336:14 347:16 373:20 381:15 382:2,6 383:22	<b>elaborate</b> 103:21 363:5 364:11 <b>elderly</b> 257:21 258:16 376:16 <b>elect</b> 178:5 <b>elective</b> 52:8 93:21 256:11 <b>electrocardiog...</b> 64:5 120:13 <b>Electrolyte</b> 229:20 <b>element</b> 119:18 <b>elements</b> 48:1 180:15 <b>elevation</b> 69:9 <b>eligible</b> 72:14 73:3 <b>eliminate</b> 256:20 <b>eliminates</b> 124:19 200:9 <b>embrace</b> 71:10 <b>embraced</b> 68:7 <b>embracing</b> 265:6 <b>emergency</b> 356:16 <b>emphasis</b> 33:6 99:9 <b>emphasize</b> 251:3 333:6 <b>emphasizing</b> 251:18 266:13 <b>empiric</b> 319:14 <b>empirically</b> 319:15 332:10 <b>employed</b> 87:1 <b>employees</b> 11:7 11:8 12:2,9,10 12:16 <b>employers</b> 12:21 <b>employment</b> 13:4 <b>employs</b> 173:7 <b>empower</b> 174:3 <b>encoded</b> 64:10 69:21 70:6 <b>encourage</b>	173:21 365:13 <b>encourages</b> 15:22 360:11 <b>encouraging</b> 366:4 <b>ended</b> 265:16 320:3 <b>endocrinologist</b> 26:9 <b>endogenous</b> 99:20 <b>endorphins</b> 236:2 <b>endpoint</b> 17:14 18:4,5 31:3 41:22 42:14,19 42:21 44:8 48:8 50:10 54:4 97:1,14 97:16 98:15 121:8 122:12 122:14,22 123:1,21 124:1 138:21 139:3,5 139:20,21 141:4 185:1,2 185:7,14,17 186:1 192:21 238:11,21 239:3 246:12 254:15 261:2 285:19 286:2 299:15 301:10 301:13,22 302:5 <b>endpoints</b> 35:13 49:17 58:7 95:3 112:21 114:15 117:14 118:4 138:14 139:9 141:19 142:7 152:10 198:6,10,13,14 214:16 222:12 222:15,18 223:10 293:6 295:6 298:21 299:6 301:21	357:14 372:7 375:15 382:4 <b>endthing</b> 128:14 <b>engendered</b> 132:5 <b>enhanced</b> 30:22 69:15 108:13 108:19 371:19 385:7 <b>enhancing</b> 236:8 <b>enjoyed</b> 211:4 <b>enlighten</b> 193:15 <b>enormous</b> 291:1 <b>enroll</b> 379:21 <b>enrolled</b> 45:4,6 51:1 59:9 138:5 145:1 256:10 263:13 371:19 385:8 <b>enrolling</b> 39:7 45:15 256:17 <b>enrollment</b> 73:3 178:7,7 <b>ensure</b> 73:10 85:7 90:4 91:14 273:19 <b>ensuring</b> 88:13 <b>enter</b> 24:20 <b>Entereg</b> 8:5 13:6 16:17 20:18 21:3,15,17,19 22:5,9,18,19 23:14 24:17 25:10 85:8,8 85:11,17 86:2 86:4 87:4,17 87:18,20 88:1 88:7 89:2,9,19 90:5,8,13 91:12,14,17,20 106:1 125:4 127:6 211:17 218:18 241:7 242:17 243:17 261:6 338:20 <b>enteric</b> 29:10 36:20 <b>enters</b> 377:15
<b>effects</b> 21:20,22 33:8 36:16 37:2,18 75:5 76:11 77:1 85:20 86:10 94:20 95:2 109:21 110:6 128:14 130:8 166:8 167:18 168:3 172:6 209:5,7 217:22 220:12 258:22 268:17 311:2 319:1 331:5 334:15,17 335:3 337:7,9 345:13 352:20 362:7 378:8 383:15	<b>effort</b> 89:15 264:14 <b>efforts</b> 89:21 363:10 <b>egg</b> 313:2 <b>eight</b> 147:22 171:11 330:1 <b>Eighty-two</b> 50:20 <b>Eisenach</b> 118:22 <b>either</b> 34:15 42:4 44:11 47:8 59:4 63:22 64:10 69:1 76:19,22 78:3 95:12 100:12 106:19 107:4 110:2 132:17 146:12 168:10 171:15 188:19 190:14 190:15 192:3 225:10 232:17 236:4,14 243:10,10,18 248:3 254:18 268:6 315:2 319:6 321:9 374:22 381:9 381:22 383:3 385:14 <b>EKG</b> 94:3 <b>EKGs</b> 93:6	<b>efficacious</b> 294:9 296:10 299:16,18 300:13 336:18 346:20 <b>efficacy</b> 13:6 16:16 17:5 18:16 21:3 22:17 23:22 24:15 25:13 35:3,7,14,19 36:9 39:12 45:1,18 46:8 46:12 48:3 72:18 74:9 84:15 98:5 99:16 112:18 114:1 115:2 134:5,10,17 136:10 137:20 138:4 139:15	<b>encourage</b> 173:21 365:13 <b>encourages</b> 15:22 360:11 <b>encouraging</b> 366:4 <b>ended</b> 265:16 320:3 <b>endocrinologist</b> 26:9 <b>endogenous</b> 99:20 <b>endorphins</b> 236:2 <b>endpoint</b> 17:14 18:4,5 31:3 41:22 42:14,19 42:21 44:8 48:8 50:10 54:4 97:1,14 97:16 98:15 121:8 122:12 122:14,22 123:1,21 124:1 138:21 139:3,5 139:20,21 141:4 185:1,2 185:7,14,17 186:1 192:21 238:11,21 239:3 246:12 254:15 261:2 285:19 286:2 299:15 301:10 301:13,22 302:5 <b>endpoints</b> 35:13 49:17 58:7 95:3 112:21 114:15 117:14 118:4 138:14 139:9 141:19 142:7 152:10 198:6,10,13,14 214:16 222:12 222:15,18 223:10 293:6 295:6 298:21 299:6 301:21	357:14 372:7 375:15 382:4 <b>endthing</b> 128:14 <b>engendered</b> 132:5 <b>enhanced</b> 30:22 69:15 108:13 108:19 371:19 385:7 <b>enhancing</b> 236:8 <b>enjoyed</b> 211:4 <b>enlighten</b> 193:15 <b>enormous</b> 291:1 <b>enroll</b> 379:21 <b>enrolled</b> 45:4,6 51:1 59:9 138:5 145:1 256:10 263:13 371:19 385:8 <b>enrolling</b> 39:7 45:15 256:17 <b>enrollment</b> 73:3 178:7,7 <b>ensure</b> 73:10 85:7 90:4 91:14 273:19 <b>ensuring</b> 88:13 <b>enter</b> 24:20 <b>Entereg</b> 8:5 13:6 16:17 20:18 21:3,15,17,19 22:5,9,18,19 23:14 24:17 25:10 85:8,8 85:11,17 86:2 86:4 87:4,17 87:18,20 88:1 88:7 89:2,9,19 90:5,8,13 91:12,14,17,20 106:1 125:4 127:6 211:17 218:18 241:7 242:17 243:17 261:6 338:20 <b>enteric</b> 29:10 36:20 <b>enters</b> 377:15

<b>entire</b> 47:13 52:18 100:19 154:11 155:8 162:12 206:21 223:16 232:10 242:13 243:6 243:16 262:4	<b>equation</b> 20:4 <b>equipoise</b> 376:5 376:14 378:4 <b>equipotent</b> 36:8 <b>equivalence</b> 229:1 <b>equivalent</b> 63:5 224:21 <b>ER</b> 290:13,14 <b>era</b> 366:21 <b>Eric</b> 5:10 25:16 61:3,5 148:8,8 228:6,7 234:12 264:4	123:17 164:8 187:10,15 197:22 207:16 223:10 229:4 242:21 248:9 249:15 320:8 364:5,8,11 <b>ethically</b> 376:8 <b>ethics</b> 11:13,20 <b>etiology</b> 28:11 162:1 165:7 220:2,10 <b>Europe</b> 23:13,16 137:15 142:9 143:6,7 220:15 230:12,13,18 231:14,18,22 231:22 232:8 294:7	74:16 76:17 85:21 94:1 134:10,20,21 138:4 139:2 140:1 144:13 148:6,11 175:6 179:15,16 183:2,14 184:6 185:8,16 189:4 193:1,7 <b>Eve</b> 290:12 <b>evening</b> 289:18 <b>event</b> 38:11 42:10 44:10 65:1 66:10,21 69:4 71:13 79:4 80:15 81:2 87:20 88:8 103:5 105:17 107:6 136:14,22 153:16 154:2 155:6 162:7 175:10 191:14 192:4 201:11 202:6 216:19 224:18 230:6 254:17 257:12 273:20 310:18 311:8,19 324:2 339:10 362:11 362:11,13 372:10,15	76:20 77:11 79:7,13,19 80:1,3,18,21 81:1,6,13,17 81:21 82:1 83:2,9,14 89:7 91:9 102:12,16 102:22 103:10 103:11 104:13 104:19 107:5 109:8 110:21 115:21 118:1 119:12,14,22 120:3,18 121:17,20 131:1,5,8,10 137:3 145:12 145:21 146:2,5 146:6,10,13,21 147:12 148:15 149:14,17,21 150:1,2,2,5,11 150:13,14,18 150:21 152:13 152:17 153:14 153:18,20 154:3,5,6,7,10 154:15,17,18 154:21,22 155:3,4,9 156:7,13 157:3 159:4,6 161:11 161:14 163:5 163:12 164:4 165:15 180:7 181:22 192:3,7 196:11,16,20 197:7,21 199:14,20 200:5,11,16,17 200:17 201:17 201:22 202:2,9 202:10 212:3 222:19 223:15 223:16,18 224:6,7,18 225:19,20 226:2,5,5
<b>enzymes</b> 36:14 <b>epidemic</b> 106:14 <b>epidemiologic</b> 64:22 361:1 362:5 363:6 366:19 <b>epidemiologist</b> 269:5 <b>Epidemiology</b> 4:7,11 10:5,7 <b>episodes</b> 174:15 <b>Epstein</b> 2:7 13:18,20 14:1 207:8,9 214:7 214:8 215:21 257:14,15,16 286:19,20 288:21 290:1,3 290:5,6 303:3 303:4 305:21 305:21 324:7,8 329:13,13 332:17,18 349:19,20 350:6 351:19 351:19 364:15 364:16 369:13 369:15 370:17 370:17	<b>erythromycin</b> 135:22 229:12 <b>especially</b> 23:5 148:8 160:4 185:18 192:5 263:20 363:17 383:2 384:1 <b>essence</b> 100:10 261:15 275:21 <b>essential</b> 12:12 <b>essentially</b> 66:17 79:17 110:9 113:4 149:19 211:22 228:9 228:12 293:19 327:7 <b>establish</b> 77:22 113:6,12 <b>established</b> 64:13 68:13 75:9 110:15,22 <b>estimate</b> 201:6 252:15 <b>estimated</b> 27:3 <b>estimates</b> 46:22 47:5 64:17 65:16 67:7 68:4 71:9 75:20 200:10 200:18 212:7 222:22 223:2 252:19 <b>estimating</b> 309:7 <b>et</b> 82:8 116:6	<b>European</b> 97:7 97:10 98:7 192:20 193:6 217:19 218:11 232:19,20 335:7 <b>Europe-limited</b> 230:13 <b>evaluate</b> 8:5 45:10 46:8 102:11 120:11 175:8 182:1 183:21 186:19 190:8 192:21 236:20 249:22 318:7 <b>evaluated</b> 37:15 38:12 40:22 44:17 83:20 95:8 129:18,21 175:11,14 241:8 <b>evaluating</b> 33:16 46:18 124:16 <b>evaluation</b> 1:2 3:20,20,22 4:4 4:6,8,10,12,14 17:13 19:22 38:9 64:20	192:20 193:6 217:19 218:11 232:19,20 335:7 <b>Europe-limited</b> 230:13 <b>evaluate</b> 8:5 45:10 46:8 102:11 120:11 175:8 182:1 183:21 186:19 190:8 192:21 236:20 249:22 318:7 <b>evaluated</b> 37:15 38:12 40:22 44:17 83:20 95:8 129:18,21 175:11,14 241:8 <b>evaluating</b> 33:16 46:18 124:16 <b>evaluation</b> 1:2 3:20,20,22 4:4 4:6,8,10,12,14 17:13 19:22 38:9 64:20	<b>events</b> 19:8 38:3 38:5 50:7 51:8 52:13 64:6,9,9 64:11,16,19 65:6,8,10,14 65:17,20,21 66:2,5,7,15 67:3,9,14,18 67:22 68:5,6 68:11,17,21 69:2,11,16,20 70:4,17,18,20 71:5,17 72:5 74:20 75:8,13 75:19,21 76:6

230:11 231:6,8 256:13 257:2 273:12,22 274:1,4 307:13 307:14,22 308:2 309:14 310:2,8,14,22 311:11 317:5,5 317:12 319:6 319:18 320:3,4 320:18 321:9 321:10 323:18 324:10 328:5,6 328:15 331:6 338:19 345:9 347:7 362:18 362:22 382:16 382:17 385:12 385:18	70:17 108:7 <b>examined</b> 38:17 166:8 187:17 <b>examines</b> 73:20 <b>example</b> 109:12 114:4 126:15 160:7 174:14 177:9 178:11 178:15 181:9 182:17 213:8 218:15 241:9 257:18 300:19 313:7 314:5 319:3 335:20 373:10 376:15 <b>Examples</b> 176:16 178:1 <b>exceed</b> 117:2 157:1 <b>excellent</b> 92:15 148:10 376:3 <b>exception</b> 11:5 51:7,14 294:6 <b>excess</b> 74:14 119:6 121:22 132:16 320:3,4 320:17 321:1 <b>excitatory</b> 29:11 <b>excited</b> 330:8 <b>exclude</b> 15:20 109:17 256:20 <b>excluded</b> 40:14 137:18 294:6 <b>excluding</b> 257:3 <b>exclusion</b> 15:21 <b>excretion</b> 166:14 <b>Excuse</b> 97:21 <b>exercise</b> 305:17 <b>exhibited</b> 209:17 <b>exist</b> 154:9 162:2 276:20 <b>existed</b> 80:20 320:5 <b>existence</b> 362:19 <b>existing</b> 368:5 <b>exists</b> 82:2 201:15 373:19 <b>exogenous</b> 99:11	99:19 130:10 <b>expand</b> 286:20 376:11 380:2 <b>expanded</b> 44:2 <b>expanding</b> 375:6 376:20 380:9 <b>expect</b> 79:11 111:4,19 131:22 218:17 219:2 221:2 229:16 253:8 274:21 318:19 <b>expectation</b> 222:5 <b>expected</b> 52:4 320:12 321:11 <b>expects</b> 270:20 <b>experience</b> 63:8 74:8 77:9 86:9 86:20 108:3 182:11 192:7 261:9 262:14 287:4 346:15 <b>experiencing</b> 62:11 201:22 <b>experiment</b> 167:14 <b>expert</b> 13:1 65:4 268:22 <b>expertise</b> 12:12 <b>experts</b> 25:8 26:1 267:12 <b>expiration</b> 176:21 <b>explain</b> 75:2 155:18 241:13 293:5 299:2 352:15 <b>explained</b> 23:18 <b>explanation</b> 91:11 283:11 <b>explicitly</b> 372:11 <b>explore</b> 72:4 <b>explored</b> 43:21 <b>exposed</b> 67:15 130:3,5 213:3 <b>exposing</b> 280:7 <b>exposure</b> 35:20	49:1 62:7 63:14 65:1 66:19 67:11 69:7 74:1,6 75:7 76:17 85:4 155:12 159:5 171:12 264:2 271:6,10 271:22 311:1 <b>express</b> 6:20 <b>expressed</b> 224:5 384:7 <b>extended</b> 30:12 181:13 231:14 <b>extension</b> 72:10 74:11 159:12 191:15 206:2,5 <b>extensive</b> 35:16 90:13 93:21 132:8 <b>extensively</b> 95:6 257:7 268:16 380:20 <b>extent</b> 103:18 161:5 194:22 229:7 <b>external</b> 65:4 71:1 131:20 264:12 267:12 <b>extra</b> 211:9 321:10 381:7 <b>extractor</b> 119:17 <b>extrapolated</b> 377:3 <b>extreme</b> 260:9 291:20 <b>extremely</b> 165:19 365:17 <b>extremities</b> 163:3	114:9 121:11 152:15 194:22 215:3 226:1 227:1 250:10 256:10 269:18 275:14 321:1 335:15 337:16 338:6 350:11 <b>factor</b> 29:7 37:5 42:7 215:13 265:19 339:18 <b>factors</b> 28:15,16 43:10 73:11 109:13 110:17 122:17 149:5 155:21 156:2 164:6 187:10 214:21 264:16 264:19 265:9 266:2 267:12 309:16 317:7 355:2 357:1 362:16,18 <b>facts</b> 86:16 <b>factual</b> 267:16 <b>failed</b> 76:7 270:9 <b>failure</b> 150:6 207:16 224:14 338:4 <b>fair</b> 6:18 <b>fairly</b> 95:19 105:13 111:17 117:13 150:21 222:21 260:15 262:20 334:14 340:18 372:5 384:11 <b>faith</b> 350:15 <b>fall</b> 162:7 164:7 254:7 331:22 339:8 <b>falls</b> 75:16 116:6 163:17 165:6 <b>familiar</b> 221:1 <b>family</b> 15:14 <b>far</b> 99:9 101:12 112:6 127:13 179:10 193:11
			<b>F</b>	
			<b>F</b> 211:1	
			<b>face</b> 214:11 244:4 313:2,2	
			<b>fact</b> 33:12 36:20 49:6 84:3 101:4 103:7	

243:11 250:13 255:20 303:5 305:5 309:17 319:11 322:12 325:19 343:15 354:1 <b>fascinating</b> 286:15 <b>fast-track</b> 136:3 <b>favor</b> 369:10 <b>favorable</b> 24:19 91:20 121:6 <b>favoring</b> 50:16 57:4 98:18 <b>FDA</b> 7:10,12,16 10:5,7,9,11,13 11:18 12:1,8 15:6,11,18,22 17:12 20:21 22:7 24:7 42:18 44:3 47:4 65:7 71:3 92:17 97:15 98:21 101:16 122:21 136:18 137:1 183:19 183:19 195:2 204:4 210:11 223:7 224:11 236:4 262:3 274:3 312:8 326:17 349:4 354:22 365:13 381:9 <b>FDA's</b> 14:16,18 134:1,4 195:21 358:14 <b>FDA-approved</b> 21:13 173:10 <b>FD&amp;C</b> 12:7 13:18 <b>fear</b> 368:7 <b>features</b> 352:15 352:21 <b>February</b> 136:4 137:8 <b>fed</b> 126:11 <b>federal</b> 4:13 7:2	9:16,17 11:4,8 11:9,13,15,20 <b>feed</b> 126:20 127:20 <b>feedback</b> 194:9 <b>feeding</b> 126:10 <b>feel</b> 34:18 90:6 91:12 97:15 109:2 112:19 113:12 115:13 122:16,20 124:17 133:16 186:2 196:4 198:17 229:10 237:20 248:21 262:11 277:6 278:19 293:9 299:12 305:7 305:14 317:17 333:11 335:22 336:4,7,9 338:18 340:21 341:19,22 344:4 345:13 351:6 354:8 374:11 <b>feeling</b> 190:15 219:14 300:10 346:18 <b>feelings</b> 348:6 <b>Feinberg</b> 6:6 <b>felt</b> 32:11 114:12 317:18 381:22 382:18 <b>female</b> 144:22 145:5 170:3,9 170:13 171:10 171:16,22 172:11 <b>fence</b> 341:5 <b>fentanyl</b> 36:18 <b>fertility</b> 172:14 <b>fewer</b> 63:12 79:5 90:16,19,20 145:16 146:5,6 268:5,7 <b>fiber</b> 167:13 207:13	<b>fibrillation</b> 364:4 <b>fibroma</b> 170:1 171:5 <b>fibrosarcoma</b> 170:1 171:5 <b>field</b> 120:8,20 <b>Fifteen</b> 292:17 292:17 <b>fight</b> 203:8 338:17 <b>figure</b> 190:20 280:1,9 357:4 368:8,9 <b>filed</b> 22:19 <b>fill</b> 372:12 <b>filled</b> 176:22 250:18 365:14 <b>final</b> 24:8 136:19 162:3 371:16 <b>finally</b> 7:19 20:2 43:11 65:3 74:12 75:21 82:18 175:3 183:11 247:6 270:16 271:4 304:10 347:10 385:5 <b>financial</b> 12:3,6 12:10,17 13:14 15:19 16:2 312:9 333:7 384:5 <b>find</b> 104:9 185:3 337:14 374:8 374:16 <b>finding</b> 59:5 74:18 100:8 302:2 309:16 <b>findings</b> 24:12 25:18,20 35:21 53:15 57:2,18 73:21 75:3 76:3 77:6,9,19 78:1 132:1 156:9,10 165:21 167:7 169:16 171:10	171:15,20,22 172:3 268:19 302:22 303:1 <b>fine</b> 125:17 378:21 <b>finger</b> 276:13,14 <b>finish</b> 181:12 286:7 359:9 381:6 <b>finished</b> 268:20 <b>firm</b> 13:22 14:5 <b>firms</b> 15:17 16:3 <b>first</b> 16:5 17:7 20:14 37:16 42:4,17 46:4 56:13 62:14 87:11 93:14 94:6 95:21 99:7 101:1 113:12 115:20 115:22 120:15 120:18 121:4 122:4 123:12 123:16 126:16 129:22 132:7 138:19,20 139:20 140:15 140:20 149:4 156:17 167:8 169:17 170:14 180:1 185:14 188:17 191:20 196:6,7 209:5 223:2,14 233:13 235:17 236:10 238:13 245:16 246:16 264:5 265:2 269:12 270:4 273:9 282:16 284:1 300:8 315:16 320:15 327:15 328:12 330:17 368:13 376:3 379:4,9 381:14 <b>Firstly</b> 110:4 <b>five</b> 17:7,18 30:9	34:8 143:16 151:8 171:6 186:16 188:17 189:22 201:16 231:6 251:11 255:9,16 260:7 275:6,9 281:6 285:17 314:5 314:10 368:4 <b>flag</b> 237:10 300:17 <b>flat</b> 316:18 <b>flatus</b> 28:6 42:4 42:10 121:8 122:10 124:19 138:20 139:2,7 185:9,16,19,21 299:1 <b>flipside</b> 380:19 <b>floor</b> 325:3 <b>Florida</b> 329:21 <b>fluid</b> 31:14 <b>focus</b> 18:2 22:16 23:7 32:22 36:1 45:1 46:4 50:17 110:18 134:11,14 185:3 187:4 190:5 250:3 318:17 365:7 <b>focused</b> 22:10 108:7,12 185:1 189:5 223:8 366:6 <b>focusing</b> 61:13 66:20 80:1 114:8 117:5 376:15 <b>folks</b> 242:10 279:4 281:3 <b>follicle</b> 70:9 <b>follow</b> 195:9 203:12 205:3 206:7 207:20 219:8 227:21 246:18 247:16 286:6 324:19 377:10
--	--	---	--	--

<b>followed</b> 52:6 83:5 131:3,12 134:20 206:17 237:2 282:13 311:14	<b>food</b> 1:1 3:18 4:2 11:1,15 42:3 42:16 135:17 138:18 289:2,3	<b>fracture</b> 64:11 74:22 84:10 137:4 162:5,11 162:18 163:3,9 163:10,15 164:1 165:8 313:13 326:9	340:11	<b>G</b>
<b>following</b> 8:7 11:11 13:10 16:19 21:16 24:17 26:1 30:20 35:10 38:6 41:3 44:16 52:16 55:11 58:20 69:18,22 78:11 79:11 82:6 84:3 95:21 126:12 135:10 176:15 208:22 273:13 307:11 307:13 328:3 351:4 382:14 383:20	<b>force</b> 90:3 362:8 <b>foresee</b> 221:19 <b>Forest</b> 2:10 <b>forgot</b> 330:7 353:11 <b>form</b> 27:12 199:13 215:14 229:11 249:18 348:20 353:1 385:13 <b>formal</b> 373:1 <b>format</b> 373:14 <b>former</b> 231:18 <b>forms</b> 108:17 <b>formulation</b> 86:14 <b>forth</b> 120:15 259:21 <b>fortunate</b> 25:7 118:13 <b>Forty</b> 51:16 <b>forum</b> 6:18 7:7 211:6 <b>forward</b> 7:22 20:9 194:11 227:7 373:15 373:18 <b>found</b> 11:14 69:8 95:14 122:13 128:21 202:21 266:6 <b>Foundation</b> 2:14 3:9 9:22 <b>four</b> 15:8 38:9 38:12 52:13 56:8 58:4 60:4 66:12 78:11 83:21 87:8 97:20 131:13 142:20 143:11 171:1 189:14 273:5,10 282:16 320:15 320:22	<b>fractures</b> 74:13 74:14 76:21 82:16 116:6 147:13 148:16 162:3,6,10,21 162:22 163:6,8 163:20 164:2,7 164:10 165:1,2 165:3,5,16 307:14 310:7 313:10 325:2 325:15 328:6 331:7 338:21 339:4 353:4 372:8 382:17 <b>fraidy</b> 344:13 <b>frame</b> 125:18 <b>framework</b> 179:20 183:12 359:19 <b>frank</b> 261:9 <b>frankly</b> 358:19 <b>fraught</b> 127:9 <b>free</b> 133:16 <b>Freedom</b> 14:22 <b>free-for-all</b> 307:17 <b>frequency</b> 52:7 65:13 68:21 75:18 79:15,19 79:21 147:6 179:17 <b>frequent</b> 80:7 111:5 <b>frequently</b> 27:9 30:18 31:15 33:1 58:21 61:12 163:2 229:21 <b>fresh</b> 289:21 <b>Friday</b> 300:19	<b>front</b> 113:12 <b>Fuchs</b> 5:3 26:6 269:4,4 <b>fulfill</b> 24:21 <b>full</b> 16:8 120:5 139:20 140:15 185:14 252:22 298:14 <b>fully</b> 14:15 77:21 <b>full-day</b> 241:2 <b>function</b> 18:9 31:2 76:9 77:2 87:9 135:15 138:16,17,19 139:12,18 143:3,21 144:4 189:21 229:11 239:5 247:10 284:8 358:9 381:18 <b>functional</b> 286:12 <b>functioning</b> 244:22 <b>funded</b> 14:12 <b>funding</b> 136:20 <b>further</b> 19:16 23:18,21 31:18 32:17 47:18 54:1 69:13 71:14 72:4 75:14 77:20 81:10 103:21 130:22 186:4,6 187:2 251:2 311:17 318:1 <b>furthermore</b> 30:16 36:12 69:8 74:2 271:16 311:12 <b>future</b> 23:7 216:8 217:13 314:1 323:3 371:19 375:1 377:19 385:8 385:20,21	<b>gain</b> 377:2 <b>gained</b> 28:10 <b>gait</b> 164:8 <b>garage</b> 348:3 <b>Garver</b> 5:4 259:8,9,9 <b>Gary</b> 2:11 5:7 26:8 250:16 <b>gases</b> 29:3 <b>gastric</b> 128:14 129:7 <b>gastroenterolo...</b> 350:1 <b>gastroenterolo...</b> 348:2,9,12 <b>Gastroenterol...</b> 2:3,11 3:22 4:3 4:5,9 10:11 <b>gastrointestinal</b> 1:6 2:19 8:4,7 10:21 11:3 13:10 16:19 29:14 86:10 89:7 134:3 166:10 208:12 <b>gather</b> 372:7 <b>gender</b> 356:22 <b>general</b> 52:9 71:5 75:10 100:9 134:10 134:17 144:12 146:18 157:13 221:12 229:4,6 285:9 294:4 340:18 385:10 <b>generalizability</b> 131:21 <b>generalizable</b> 133:9 <b>generally</b> 42:7 62:2 63:9 77:11 81:4 82:11 171:22 229:5 256:12 273:5

<b>generic</b> 337:11	193:1 203:15	<b>GI-1-2</b> 296:10	25:17 61:6	148:13 157:10
<b>genetic</b> 172:8	208:14 216:19	<b>GI-2</b> 18:3 42:15	234:13	172:20 183:17
<b>genotoxic</b>	229:11 237:21	42:18,20 50:11	<b>global</b> 65:5	210:16 211:8
166:19 270:8	241:20 243:18	53:10,20 54:2	343:5,10	211:12 212:8
<b>genotoxicity</b>	244:4,9,10	54:11 59:19	350:17	212:12,15
168:21 169:1	246:4 247:10	96:10 97:14	<b>go</b> 27:11 60:21	213:16 225:16
271:8	275:1 276:12	98:15 101:21	99:22 112:4	226:18 236:11
<b>genotoxicology</b>	284:8 381:18	114:16 121:5	173:9 184:9	239:10 240:12
166:22	<b>Ginny</b> 5:12	121:10 122:5,9	187:2 191:15	243:11 244:1,2
<b>gentle</b> 6:21	274:9	122:21 123:7	204:3 205:15	244:9 245:16
<b>gentlemen</b> 92:4	<b>give</b> 16:13 20:18	123:22 124:3	205:17 225:22	247:1 249:9
118:17 127:17	26:19 116:10	124:17 139:1,3	237:10 240:9	259:7 260:11
<b>geography</b>	128:9 189:8,21	139:4 141:3,3	244:20 247:18	260:19 267:16
230:12	195:10 201:5	141:8 143:3,22	248:11 250:18	271:11 275:5
<b>George's</b> 26:4	232:5 236:15	144:4 185:2,7	254:1,22	275:10 278:12
118:18	249:12,14	185:13 186:1,2	257:17 279:13	283:17,18
<b>George's</b> 4:18	262:10 267:16	192:22 236:16	286:1 289:6,10	286:16,22
<b>getting</b> 96:1,2	274:7 275:9	239:21 246:12	289:20 295:16	287:12 292:6
98:9 103:20	278:13 279:2	258:8 260:19	298:10,12	292:22 296:20
128:4 129:13	279:14 280:18	261:1 262:12	299:11 300:19	298:7,13 300:7
279:7,7,10	330:17 336:17	284:6 286:2	303:13 304:1	300:16,21
288:5 291:17	356:4,17	293:6 295:6	319:14 321:16	301:6 302:10
291:18 295:17	365:20 366:1	298:22 299:11	322:12 338:15	303:21 304:1,1
296:12 355:16	381:11	299:15,19	350:19,20	304:3,4,5
379:1	<b>given</b> 23:20	301:22 302:16	357:13 369:2,4	305:18 306:22
<b>get-go</b> 253:17	70:15 73:4	337:18 343:9	369:14	307:5 312:19
<b>GI</b> 10:9 18:9	76:17 83:4	381:16,20	<b>goal</b> 6:17 85:7	315:4,11 320:9
21:21 22:3	91:8 98:4	382:2	174:11,14,17	320:9,13 323:2
29:3 37:18	138:7,12 158:4	<b>GI-3</b> 18:2 42:1	<b>goals</b> 112:6	324:6 325:10
41:1,17,19	164:2 203:15	48:8 50:10	173:6,8 174:10	325:12 327:11
42:2,3,12 43:5	222:15 226:3	53:20 54:4,18	174:22 179:14	327:20 330:3
43:22 44:14	245:11 254:4	121:7,9 122:5	183:1	330:17 331:9
49:4,6 50:14	255:19,21	122:9 123:3,6	<b>goes</b> 218:21	331:16 338:16
52:7,11 53:3	264:13 271:13	123:11 124:1,3	220:2 276:6	338:16 339:7
54:13 55:2,9	272:1 300:9	138:14,20	305:5 319:11	339:19 341:20
55:22 59:11	308:9 312:7	139:1,5,18,19	355:7,9,9	348:2,9 349:16
90:15 94:20	316:5 357:16	140:5 143:3	<b>going</b> 6:4,7 8:3	350:19,20
95:2,3 98:15	364:8 374:7,7	144:4 185:2,3	10:15,17 16:4	352:9 355:12
100:12 104:18	375:19	185:6 192:22	16:13 20:17	359:8,9,10,19
105:22 116:17	<b>gives</b> 209:22	239:21 246:12	60:21 78:11	360:16 361:18
123:2 128:20	211:9 220:6	260:20 261:3	92:5 93:15	362:11,12,15
129:3 134:8	233:15 321:7	284:6,11 293:7	106:6 109:17	362:17 363:7
135:9,14	<b>giving</b> 138:8	299:1 337:18	111:15 113:2	367:3,17,19,20
138:16,17,19	336:9 363:1	381:17,21	114:6 118:12	368:2,11 369:4
139:12,17	<b>GI-related</b>	<b>Glasgow</b> 231:9	122:6 126:7	369:18,19
143:2,7,21	216:15	234:3	127:1 130:6,14	371:11,15
144:4 146:5,6	<b>GI-1</b> 284:11	<b>GlaxoSmithKl...</b>	130:17 133:13	377:1,16 379:5
146:8 189:20	293:6	5:11 22:12	133:22 134:1,4	379:10 380:5

381:6,11 385:22 <b>good</b> 6:3,10 9:18 10:19 20:19 35:4 60:17 61:6 118:16,17 134:6 148:13 165:22 173:17 207:4 211:3 223:1 283:2 284:22 296:5 338:14 346:18 353:17 356:15 373:20 376:18 380:15 <b>government</b> 7:3 11:7 12:2,9,10 12:15 <b>Grand</b> 26:18 213:20 <b>grant</b> 12:1,8 <b>granted</b> 13:20 14:3,10 136:4 311:4 <b>grants</b> 13:2 <b>graphs</b> 224:4 <b>gray</b> 52:22 <b>great</b> 198:7 203:4 213:1 332:22 334:9 337:20 <b>greater</b> 31:12 36:22 48:20 51:18 53:21 55:4 56:22 59:9 63:1,3 74:1,9 86:9 108:20 158:14 159:1 227:3 258:1,9,10 266:9 314:10 357:5 375:12 <b>greatest</b> 313:12 <b>greatly</b> 212:1 <b>Greece</b> 233:18 <b>green</b> 153:11 <b>gross</b> 264:9 <b>group</b> 47:11	49:9 51:6 53:20 57:14 61:5 65:12 70:6 73:15,18 74:2,10 79:10 79:20 80:7 81:2,9 96:15 96:16 99:17 104:4 105:2,3 105:11 106:1 114:21,22 119:19 121:18 122:1 140:4,7 141:7,10,21 142:1,14,16 143:13,14 145:6,10,13,14 146:3,15,22 147:1 149:16 149:18 150:18 150:19 154:19 155:1,4,9 157:7 158:1,3 159:18,20,21 159:22 160:4 161:1,2 163:6 163:13,21 164:13 165:4,5 188:19 194:7 199:19 217:16 217:21 220:11 226:2,3 241:9 258:3,13 265:15 266:18 267:1,7 269:7 291:14 321:10 337:10 367:6 375:7,16 <b>grouping</b> 70:17 <b>groups</b> 50:14 51:16 52:3 54:11 64:15 68:7 73:12 79:18,22 80:9 82:2,21 94:3 102:12 103:16 106:22 142:11 144:22 145:7	145:18 146:3,6 146:7,14 149:7 149:8,11,20 150:10,22 153:21 154:9 154:14 157:2 157:16 159:16 160:6,18,20 161:8,17,22 162:14,17 163:11 164:6 164:12,17,21 165:9 170:17 187:19 190:13 200:8 215:10 215:16 229:15 230:4,7 243:15 250:7 252:2 262:22 264:22 302:14 376:4 376:12 381:2 <b>growth</b> 236:6,8 <b>GSK</b> 19:6 23:12 60:22 71:3 119:11 228:7 261:15 264:4 274:8,10 338:19 <b>GSK-sponsored</b> 61:2 <b>GSK014</b> 24:4,9 25:18 61:3 80:12 82:15 88:19 91:7 120:9,18 225:2 225:14 309:2 <b>guess</b> 93:11 117:11 121:19 131:18 188:18 199:10 215:21 217:8 227:17 266:4 295:2 298:4 318:16 330:6 336:21 356:15 <b>guesstimate</b> 297:4 <b>guests</b> 20:22	26:14 <b>guidance</b> 220:6 261:12 <b>guide</b> 177:4 <b>guidelines</b> 81:20 <b>guides</b> 176:6,7 <b>gut</b> 36:7 208:14 213:5 339:16 <b>guys</b> 238:4 244:3 359:21 <b>GY</b> 160:11 <b>GYN</b> 160:11 <b>gynecological</b> 296:22 297:6 <hr/> <b>H</b> <hr/> <b>H</b> 3:4 <b>hair</b> 70:9 <b>half</b> 288:2 295:22 297:1 301:15,17,19 <b>halfway</b> 119:3 <b>half-day</b> 235:12 <b>half-hour</b> 138:7 <b>half-life</b> 135:6 <b>halls</b> 290:15 <b>hallways</b> 290:15 <b>hampered</b> 74:21 <b>hamster</b> 169:7 <b>hand</b> 92:8 260:6 278:22 280:18 296:22 304:4,6 304:11 305:15 305:16 306:17 323:12 329:8 341:14 351:8 369:12 370:9 371:9 <b>handle</b> 339:15 339:19 <b>handles</b> 226:16 <b>hands</b> 306:6 328:16,18 361:20 370:13 <b>hanging</b> 321:14 <b>haphazardly</b> 358:21 <b>happen</b> 291:5	345:22 381:4 <b>happened</b> 151:1 350:12 <b>happening</b> 237:1 <b>happens</b> 28:13 324:1 <b>happy</b> 201:14 232:1 233:2 269:1 <b>hard</b> 107:6 283:15 294:17 309:2 319:9 341:8 379:1 <b>harder</b> 332:6 376:10 <b>hardest</b> 301:22 <b>harm</b> 309:21,22 343:16 344:5 <b>hat</b> 321:14 <b>hate</b> 302:21 <b>hazard</b> 46:21 50:11 53:19 54:2,9,21 55:15 56:21 58:5 114:14 124:6 140:10 141:12 142:2 265:3 266:12 267:9 <b>hazards</b> 46:19 47:6 <b>head</b> 160:8 <b>heads</b> 237:10 <b>healing</b> 27:20,22 <b>health</b> 2:6 3:15 5:13 8:18 21:8 26:18 34:17 41:8 87:3 89:16 90:10 174:6,13 175:7 175:8,21 176:2 176:3,15 177:11 178:3,5 178:10 179:1 213:20 322:21 333:1 342:10 355:22 360:10
---	---	---	---	--

<b>healthy</b> 274:21 332:5,6,10	341:7 345:17 352:1,1 360:3 360:3 370:19 370:19 375:13 380:18,19	215:19 <b>high-dose</b> 376:13 <b>high-risk</b> 173:20 379:3 380:10	49:8 55:13 59:13,20 85:9 86:5,18 88:1 89:10,14,20 90:3,3,8,16,21 91:1,17 100:10 100:13,18,21 101:5,7 102:3 106:10 107:17 112:21 131:17 132:18,22 138:10,13 139:11 141:18 143:6,10,12,15 144:1 148:1 151:2,4 178:12 180:19 181:5 181:13 190:7 193:8 216:18 218:4 229:5 238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	181:10 182:6,9 183:8 239:5 288:10 312:12 337:3 339:15 356:13 359:16 364:6 <b>hospital's</b> 340:7 <b>hot</b> 289:3 307:16 <b>hotels</b> 239:5 <b>hour</b> 211:10,19 212:18 239:6 290:18 291:18 <b>hours</b> 38:22 50:15,15 52:15 53:12,13 54:10 54:12 56:2,11 56:18,19 57:8 57:10,11 95:21 97:20 98:1,1 112:14 135:5,6 138:7 140:9,10 141:8,9,11,12 141:22,22 143:21 185:20 233:13 239:4,6 239:7,8,12,13 240:11 248:17 251:5,6,7,8 252:15,16,18 252:19 253:19 254:6 271:18 275:5 276:7 284:12,13,13 285:9,13,18 286:2,3 288:3 288:16 289:11 290:22 291:15 291:22,22 292:5,16,20 295:12,19 296:2 299:9,10 300:11 332:4 333:2,2 340:8 340:14,14,17 341:18,19 355:21 <b>house</b> 289:19 <b>huge</b> 287:18
<b>heard</b> 37:4 41:6 83:19 131:2,11 187:7,11 193:13 217:6 237:8 278:22 297:12,17 315:4 324:15 348:11,12 349:21 350:7,8 350:9,18 358:5 369:3	<b>Hennessy's</b> 334:5 366:14 <b>hERG</b> 167:10,11 <b>heterogeneous</b> 70:7 <b>Hi</b> 109:1 235:3 269:4 274:9 <b>high</b> 73:2 75:10 88:12 96:2 111:20 166:5 171:1,7 174:2 210:15 221:14 222:6 226:4 231:10 234:3 234:22 275:18 375:8,16 378:13,16,21 379:12,20,21 <b>higher</b> 30:2 32:19 48:20 49:2 51:5,9,11 51:20 52:1 53:2,7 55:1 57:13 59:17,18 62:4,10 104:3 108:16 111:1 113:18 157:18 158:1 160:21 161:11 164:13 164:15 180:10 215:22 255:13 274:20,22 322:2 362:13 <b>highest</b> 50:22 53:17 169:21 170:6 177:14 221:9 <b>highlighted</b> 48:12 89:11 140:16 141:5 142:9 <b>highly</b> 36:4 37:18 86:11	<b>hint</b> 319:16 <b>hip</b> 163:1 165:2 <b>histologic</b> 270:21 <b>histologies</b> 270:18 <b>histology</b> 270:16 <b>history</b> 120:14 134:16 136:1 <b>hitting</b> 339:5,6,6 <b>hoc</b> 43:1 48:9 198:12,13 299:20 <b>hold</b> 137:2 <b>holds</b> 180:2 <b>home</b> 181:12 227:11 240:9 244:20 245:7,9 245:16 246:22 288:21 289:6,8 289:21 300:4,7 300:16,19 <b>homes</b> 181:8 361:21 <b>honest</b> 262:13 <b>Hong</b> 268:9 <b>hope</b> 108:18 120:21 133:11 211:4 <b>horizontal</b> 252:6 253:4 <b>hormones</b> 28:17 <b>horse</b> 355:8 <b>hospital</b> 4:18 18:8 21:11 22:3 26:4 27:8 29:22 30:3,12 31:10,12,20 32:9,16 33:14 38:2 41:5 43:3 43:8 44:12	181:10 182:6,9 183:8 239:5 288:10 312:12 337:3 339:15 356:13 359:16 364:6 <b>hospital's</b> 340:7 <b>hot</b> 289:3 307:16 <b>hotels</b> 239:5 <b>hour</b> 211:10,19 212:18 239:6 290:18 291:18 <b>hours</b> 38:22 50:15,15 52:15 53:12,13 54:10 54:12 56:2,11 56:18,19 57:8 57:10,11 95:21 97:20 98:1,1 112:14 135:5,6 138:7 140:9,10 141:8,9,11,12 141:22,22 143:21 185:20 233:13 239:4,6 239:7,8,12,13 240:11 248:17 251:5,6,7,8 252:15,16,18 252:19 253:19 254:6 271:18 275:5 276:7 284:12,13,13 285:9,13,18 286:2,3 288:3 288:16 289:11 290:22 291:15 291:22,22 292:5,16,20 295:12,19 296:2 299:9,10 300:11 332:4 333:2,2 340:8 340:14,14,17 341:18,19 355:21 <b>house</b> 289:19 <b>huge</b> 287:18	
<b>heart</b> 69:6 77:14 81:18 150:6 168:12 207:16 224:14 259:14	<b>heavy</b> 342:9	<b>hold</b> 137:2	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	
<b>heart</b> 69:6 77:14 81:18 150:6 168:12 207:16 224:14 259:14	<b>heavy</b> 342:9	<b>hold</b> 137:2	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	
<b>held</b> 6:17 16:7	<b>help</b> 25:8 101:12 127:2 144:8 236:3 247:1,5 247:13 250:11 250:14 272:13 336:15	<b>home</b> 181:12 227:11 240:9 244:20 245:7,9 245:16 246:22 288:21 289:6,8 289:21 300:4,7 300:16,19	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	
<b>helped</b> 261:22	<b>helpful</b> 203:22 294:21 374:16	<b>honest</b> 262:13	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	
<b>helping</b> 343:5	<b>helps</b> 291:8	<b>Hong</b> 268:9	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	
<b>HENNESSEY</b> 213:1	<b>Hennessy</b> 2:21 9:18,19 13:19 14:3,6 195:16 212:21 255:18 255:19 256:7 301:8,9 306:3 306:3 307:20 307:21 315:20 327:2,3 329:6 329:6 333:13 333:14 335:13	<b>hope</b> 108:18 120:21 133:11 211:4	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	
<b>Hennessy</b> 2:21 9:18,19 13:19 14:3,6 195:16 212:21 255:18 255:19 256:7 301:8,9 306:3 306:3 307:20 307:21 315:20 327:2,3 329:6 329:6 333:13 333:14 335:13	<b>highest</b> 50:22 53:17 169:21 170:6 177:14 221:9	<b>horizontal</b> 252:6 253:4	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	
<b>highlighted</b> 48:12 89:11 140:16 141:5 142:9	<b>highly</b> 36:4 37:18 86:11	<b>hormones</b> 28:17	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	
<b>highly</b> 36:4 37:18 86:11		<b>horse</b> 355:8	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	
		<b>hospital</b> 4:18 18:8 21:11 22:3 26:4 27:8 29:22 30:3,12 31:10,12,20 32:9,16 33:14 38:2 41:5 43:3 43:8 44:12	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	
		<b>hospitalization</b> 31:19 32:15 119:16 135:19 254:19 285:12	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	
		<b>hospitals</b> 4:20 26:6 87:15 106:15 108:14 178:8 180:16 180:18 181:7,8	238:14,19 240:12,16 245:5,12 246:15 271:17 273:17 276:15 278:9 286:4 287:8,13,15,16 287:20 288:2,6 288:8 290:8,9 290:11,14,20 291:4 297:5 301:15,16 303:6 311:14 332:3 333:16 338:13 340:9 340:18,20 341:1 345:22 347:12,21 359:13,14,14	

324:17	189:1 196:8	261:13 271:16	49:14 59:4	313:21 319:13
<b>human</b> 26:16	210:8 213:13	275:8,10,14,17	60:9 101:6	336:2 341:20
171:11,21	366:20	276:9,10,16	124:16 128:22	364:1 378:8
299:3	<b>idiopathic</b>	277:1 278:8	130:6 243:12	382:3 383:2
<b>humans</b> 76:15	223:22	284:6 286:10	265:22 288:15	<b>Importantly</b>
<b>hunch</b> 365:19	<b>IDMC</b> 69:5,16	294:20 296:21	319:1 358:7	66:9
<b>Hungary</b> 268:6	117:20,21	308:4 332:19	<b>impacted</b> 214:15	<b>impractical</b>
<b>hydration</b>	118:14,20,21	345:1 357:21	229:11	324:14
246:22	225:21 268:16	381:16	<b>impacts</b> 129:7	<b>impression</b>
<b>hyperlipidemia</b>	268:18	<b>illness</b> 15:14	<b>impair</b> 29:3	18:15 195:21
75:12	<b>IDMC's</b> 68:19	73:6	<b>impairment</b>	<b>improve</b> 29:22
<b>hypertension</b>	<b>ignorance</b> 366:7	<b>illuminate</b> 19:16	135:14	68:14
75:11 79:17	<b>ignore</b> 313:6	<b>illustrate</b> 289:10	<b>impairs</b> 28:1	<b>improved</b> 27:20
149:10	<b>II</b> 38:13 78:16	<b>illustrated</b> 90:17	270:3	<b>improvement</b>
<b>hysterectomies</b>	153:6 231:6	272:16	<b>implausible</b>	91:2 101:17
296:20	375:1	<b>imbalance</b> 64:11	270:13	184:2 332:22
<b>hysterectomy</b>	<b>III</b> 22:20 35:7	66:14,22 67:21	<b>implement</b>	<b>improves</b> 238:1
17:20 23:1	37:12,14 38:14	68:2 69:19	348:20 385:19	<b>improving</b> 240:7
40:7 45:15	40:5 48:1	72:5 73:16	<b>implementation</b>	332:12
78:19 99:16	78:17 137:10	74:13 80:11	60:2 179:15	<b>imputed</b> 12:18
100:4,7 101:3	153:6 373:12	82:1,15 88:19	183:2	15:19
137:14,21	375:1	110:5,20	<b>implemented</b>	<b>inability</b> 135:16
145:3 245:8	<b>ileostomy</b> 40:16	153:20 155:19	39:17	<b>inadequate</b>
297:2,7	<b>ileus</b> 17:8 19:2	156:6 157:22	<b>implications</b>	311:4 370:12
	21:5,6 22:10	158:5 159:15	156:14	383:1
<b>I</b>	22:16 26:21,22	161:13,16	<b>implied</b> 102:4	<b>inappropriate</b>
<b>IBD</b> 314:8	27:6,7 28:2,11	164:5 165:8	<b>imply</b> 152:16	86:4,22
<b>ice</b> 375:5	28:12 29:1	196:16 224:22	<b>importance</b>	<b>inaudible</b> 142:5
<b>idea</b> 186:9	30:3,11 33:12	225:6 234:16	85:10 278:20	142:12 167:2
195:14 232:6	34:12,16,19	234:17 264:9	<b>important</b> 20:2	208:10 209:12
245:10 270:13	35:10 36:3	265:11 282:8	44:19 86:1	209:13,14,15
274:10 332:14	37:7 51:12	319:18	87:11 100:5,8	209:19,21
355:22 358:2	53:7 58:10	<b>imbalanced</b>	102:7 111:14	<b>incentive</b> 368:3
362:12	66:8 91:13	164:11	120:16 130:7	<b>incidence</b> 30:2
<b>ideal</b> 30:5 314:8	93:5 104:22	<b>imbalances</b>	152:10 175:12	41:14 51:11
<b>identified</b> 29:6	105:7 117:7,10	71:14,15 80:19	178:20 190:19	58:15 60:6
66:16 70:21	135:13 145:16	91:6 147:12	211:11 236:18	65:8 67:4,17
75:2,5 87:16	193:21 194:2,4	157:15 160:5	238:3,3 239:16	68:6 69:10,21
91:12 120:1	216:1 217:5	160:16 265:20	240:17 244:13	81:8 82:5,10
136:14 137:5	219:15,19	<b>immediate</b> 88:9	245:19 250:3	103:11,15
146:22 147:13	220:3,10,13	201:18	260:8,13,16	121:15 157:13
148:16 156:19	221:4,10,20	<b>immediately</b>	261:17,18	161:11 162:12
162:5 168:14	226:22 227:4	103:5 128:8	262:6,7 276:18	170:22 231:11
196:12,15	228:19 230:1	233:1	280:9 287:5	234:3 346:17
210:15 353:3	235:8 237:2	<b>immune</b> 235:20	291:16 293:9	<b>incidences</b> 68:17
361:7	238:22 240:6	263:4 269:19	295:19,22	146:19 170:1,8
<b>identify</b> 7:16	240:19 242:11	270:3	299:5 300:11	170:13,19,21
76:7 120:11	254:18 257:22	<b>impact</b> 21:7	301:1 302:3	171:1,6,13

277:21	<b>inconvenience</b>	19:14 22:11,13	<b>infarcs</b> 82:10	355:15,20
<b>incident</b> 82:20	361:10	22:16 45:1	88:19	356:8,18 357:4
<b>incision</b> 222:6	<b>incorrect</b> 219:17	62:20 77:12	<b>infarction</b> 65:17	366:18 367:6
<b>incisions</b> 227:11	<b>increase</b> 65:9,11	85:12 92:1	66:21 82:6	380:16
<b>include</b> 12:22	66:15 81:1	134:12,15	119:7 120:3	<b>informed</b> 174:5
45:20 47:19	154:5 156:13	135:8,12,21	150:3 198:6	177:13 312:16
69:15 88:6	159:5 164:7	136:4,7 138:1	224:12 256:14	358:4
90:19 135:18	179:3 186:21	147:11 148:2	256:22 257:10	<b>infrequently</b>
135:22 166:6	265:13 266:13	148:20,22,22	316:2	300:5
175:6 176:17	266:17 270:1	165:13 184:12	<b>infarctions</b> 64:8	<b>infusion</b> 178:8
177:4,21	279:18 360:12	189:17 219:21	65:12 66:10	209:13
179:13 184:17	<b>increased</b> 62:13	221:13 271:5	68:2 80:11	<b>inhalational</b>
186:17 191:4	75:15 84:10	276:19,22	110:11 132:10	29:2
193:1 223:21	85:19 107:21	277:18 293:17	228:10 234:15	<b>inherent</b> 302:9
223:22 231:17	155:11,11	294:12 298:5	282:16	<b>inhibit</b> 29:13
231:18 274:3	159:5 257:9	319:22 321:15	<b>infection</b> 32:2,2	<b>inhibition</b> 129:4
338:7 364:21	263:3 266:22	321:17 322:1	34:3 103:1,2	167:11 236:6
<b>included</b> 15:4	267:3 313:9	335:9 337:13	103:15 276:3	<b>initial</b> 38:8,14
17:20 22:20	345:2 347:6,9	352:12 357:15	345:21	41:21 52:15
45:18 46:15	364:19	369:21 373:10	<b>infections</b> 30:14	66:10 83:21
50:19 64:20	<b>increases</b> 41:11	373:11,13,18	101:22 103:3	114:7 123:22
66:18 75:20	75:12 160:2	374:20 376:19	106:11 271:19	136:2 138:6
123:4 138:3	256:21,21	378:4 380:2,6	278:6	184:19 265:2
144:14 145:2	<b>increasing</b> 28:20	380:9 384:15	<b>Infectious</b> 3:11	356:2
150:5 216:15	357:22	<b>indications</b>	9:2	<b>initially</b> 37:14
216:17 294:5	<b>incremental</b>	18:13 22:8	<b>inflammatory</b>	145:2 189:5
343:4 382:5	201:17	144:11 149:3	28:21 220:12	190:4
<b>includes</b> 78:14	<b>increments</b>	194:5 375:2	<b>influence</b> 43:9	<b>initiated</b> 39:21
78:18 144:15	291:6,13	376:11 385:21	265:8	<b>initiation</b> 66:12
169:1 192:18	<b>IND</b> 136:2	<b>indicator</b> 223:1	<b>influencing</b>	<b>injure</b> 339:8
246:5,13	<b>independent</b>	<b>indicators</b>	267:14	<b>innervate</b> 29:12
<b>including</b> 12:18	68:12 77:14	287:20	<b>information</b>	<b>inpatient</b> 22:11
28:4,15 30:13	81:11 150:12	<b>individual</b> 53:16	11:11 14:22	179:22 181:14
70:7 76:12	<b>independently</b>	65:13 68:5,15	19:15,21 47:17	183:10 357:11
78:12 112:21	45:11	70:5 212:2	61:1 87:22	363:19
133:6 168:2,10	<b>index</b> 64:20	248:7 255:10	118:15 165:6	<b>input</b> 20:6 33:2
176:1 208:5	<b>indicate</b> 143:11	255:12 291:11	182:1 193:10	262:14 328:12
273:22 317:7	283:2 325:7	310:9	202:19 203:4	338:7 356:9
324:5 359:15	<b>indicated</b> 74:5	<b>individuals</b> 6:20	203:22 204:15	<b>insert</b> 177:5
<b>inclusion</b> 40:3	77:16 121:14	6:22 14:14	206:9,14,18,21	<b>inserted</b> 125:2
64:4 69:22	138:17,19	164:14 214:11	212:17 228:5	125:14,18
71:11,21	184:13 185:5	<b>individual's</b>	232:2,3 233:2	<b>insertion</b> 31:6
<b>inclusion/excl...</b>	354:5	12:5	250:5 263:22	41:10,15 58:10
379:15	<b>indicates</b> 53:1	<b>induction</b> 37:20	264:1 278:2	58:16 60:7
<b>incomplete</b>	145:22	<b>industry</b> 11:6	309:5 311:10	121:15 125:7
305:7 319:17	<b>indication</b> 13:8	15:7,8 88:12	311:17 312:3,9	125:10 127:6
<b>inconsistent</b>	16:17 17:1,4,9	358:9	314:18 316:22	<b>insertions</b> 90:20
131:14	17:11,14 19:2	<b>ineffective</b> 101:3	322:11 323:4	122:6

<b>inserts</b> 176:7	81:6 251:14	<b>intestine</b> 126:22	<b>ischemic</b> 69:1,6	374:19 376:6
<b>instability</b> 164:8	254:15	<b>intolerant</b> 62:10	77:14 120:3	385:14
212:6 223:2	<b>interested</b> 18:12	<b>intravenous</b>	149:22 150:2	
319:8	19:18 102:8	29:3 32:1	153:19 154:7	<b>J</b>
<b>instance</b> 114:20	106:5 201:7	<b>intrinsic</b> 99:12	154:10,17	<b>J</b> 2:18
343:4	327:13 337:9	<b>introduce</b> 6:7	155:2 200:4,17	<b>Jackson</b> 5:6 25:5
<b>instances</b> 70:7	<b>interesting</b> 7:22	8:12 10:15,15	202:9,10	25:14,19 60:14
<b>institute</b> 3:11	18:19 107:2,22	16:5	223:10,15	60:17,18 61:5
5:3 9:2 26:7	110:20 113:9	<b>introduction</b>	224:7,8,11,14	78:6,8 93:13
81:12 88:4	132:21 194:7	16:14 20:18	224:16,18	110:4 111:16
117:9 269:6	195:14 215:1	283:4	225:19,20	113:2 115:3
364:6	258:6 349:2	<b>Invasive</b> 2:19	319:6	116:10,22
<b>instituted</b> 294:2	<b>Interestingly</b>	<b>investigate</b>	<b>isolated</b> 167:13	118:12 122:3
<b>Institutes</b> 3:15	105:8 162:21	264:17	259:1 316:18	132:4 213:15
8:18	<b>interests</b> 12:22	<b>investigation</b>	<b>issue</b> 13:22 16:3	213:15 214:17
<b>institution</b> 8:12	13:14	77:21 203:5	24:7 99:8	223:11 226:18
298:1	<b>interim</b> 24:4	<b>investigator</b>	106:7 116:5	256:5 259:7
<b>institutions</b>	196:17	40:13 44:11	149:2 186:22	263:15 268:12
133:7	<b>intermediate</b>	104:15 105:1	193:17 194:3	268:12 281:11
<b>institution's</b>	174:12,17	151:12,17	196:10 233:4	281:11 282:1
238:15	<b>internal</b> 2:9 65:4	205:8	233:19 235:18	282:15,22
<b>instructed</b>	<b>interplay</b> 28:14	<b>investigators</b>	235:19 276:17	283:14
273:21	<b>interpret</b> 159:3	198:4 230:19	276:18 280:15	<b>JAMA</b> 107:13
<b>insufficient</b>	160:2 292:2	232:20,21	280:17 281:4	<b>January</b> 1:22
136:10	294:14	<b>investments</b>	327:16 328:13	10:22
<b>insurance</b>	<b>interpretation</b>	13:1	364:12 365:17	<b>Jay</b> 2:13 9:3
300:17	49:16 69:17	<b>invite</b> 26:11	375:19 379:22	99:5 318:6
<b>intact</b> 259:3	150:14 188:12	60:22	<b>issued</b> 13:16	<b>jejunostomies</b>
<b>intake</b> 27:17	<b>interpreted</b>	<b>invited</b> 15:9	14:9 23:20	126:10
246:21	253:7	<b>involve</b> 15:16	136:18 140:20	<b>Jim</b> 118:22
<b>integrate</b> 296:1	<b>interruption</b>	33:3 191:6	196:9,12	<b>job</b> 359:22
<b>integrated</b> 52:12	6:21 304:18	<b>involved</b> 29:2	<b>issues</b> 6:19 43:11	<b>Joe</b> 8:19 228:17
58:4 65:3	<b>interval</b> 124:8	89:16 90:1	91:4 93:16	<b>JoELLEN</b> 2:17
<b>integrating</b>	325:18 326:20	220:3 230:19	148:14,16	9:8 338:11
67:20 253:3	326:22	233:10 335:6	153:10 174:7	354:19
<b>intended</b> 17:3	<b>intervals</b> 54:22	337:2	196:8 197:5	<b>John</b> 4:16,18
72:10 364:20	58:6 64:18	<b>involvement</b>	222:1 277:17	26:2,3 118:18
<b>intense</b> 33:2	65:15 67:5	15:21	287:9 333:7	256:8
<b>intention</b> 216:13	68:4,7 81:3	<b>involves</b> 13:5	374:9	<b>joined</b> 25:22
<b>intent-to-treat</b>	154:21 155:3	58:10	<b>issuing</b> 14:16	<b>joint</b> 221:16
46:9 253:18	<b>intervention</b>	<b>in-hospital</b>	<b>item</b> 244:13	<b>joke</b> 289:10
254:4	28:14 41:18	32:19 152:6	<b>it'd</b> 203:22	<b>Joseph</b> 2:18 14:9
<b>interest</b> 10:18,20	58:8 179:2	331:13 351:3	286:14	<b>journal</b> 107:13
11:10,13,21	317:10 345:10	383:19	<b>IV</b> 40:10 48:17	<b>Joyce</b> 4:9,11
12:6,17 13:16	<b>interventions</b>	<b>ion</b> 36:15	48:22 58:22	10:6,10 16:9
14:8 15:19	27:10 30:19	<b>Iowa</b> 8:20	95:20 96:8,12	211:14
17:12 44:8	<b>intestinal</b> 27:16	228:18	168:5 373:1,2	<b>judge</b> 254:12
77:7 80:16,22	29:12 80:4	<b>IPAA</b> 314:9	373:3,7,11	<b>judgment</b> 81:20

120:4 300:3	<b>kids</b> 133:17	311:9 312:20	299:17 304:19	251:12
<b>Judith</b> 3:3 9:14	<b>killing</b> 323:20	313:19 321:5	304:22 306:12	<b>landmarks</b>
94:15 220:19	<b>kilogram</b> 168:5	322:22 323:21	306:21,21	251:9
247:15 336:12	169:22 209:20	325:3 332:9	310:20,21	<b>laparoscopic</b>
<b>Julie</b> 3:19 10:12	<b>kilograms</b>	336:15 339:4	318:1 322:5,6	227:3,10
<b>July</b> 136:9	167:20 168:16	344:2,6 347:22	329:4,4 335:1	<b>laparoscopic...</b>
<b>June</b> 136:8	168:18 169:13	353:19 355:4,5	335:2 352:3,3	298:3
	169:15 170:7	355:12 363:9	357:7,8 366:12	<b>laparotomy</b> 40:8
	209:8	366:3 373:13	366:14 367:22	220:9 221:8
<b>K</b>	<b>kind</b> 156:20	376:8,22	370:21,21	298:7
<b>Kaplan-Meier</b>	195:3 197:17	378:16 379:9	<b>Krist</b> 3:4 8:21	<b>large</b> 8:8 13:11
47:3 52:10	203:7 205:6	379:12	8:21 130:14,19	16:20 17:21
56:9 96:11,18	212:9 230:15	<b>knowing</b> 372:2	130:20 277:11	32:5 33:14
197:21 236:17	236:1 249:8	<b>knowledge</b>	277:13 280:14	34:1 40:6 45:3
240:3 241:19	261:15 287:3	28:10,20	281:22 282:12	51:21 82:12
243:14 250:19	326:15	175:15	282:20 283:6	84:11 128:22
251:22 252:4	<b>kinds</b> 178:1	<b>known</b> 29:9	290:2 291:2,3	129:5 133:5
<b>kappa</b> 36:12	196:20	126:9 196:3	292:10,15,19	135:10 137:13
259:15	<b>knew</b> 236:22	231:7 311:5	296:14 299:9	153:9 154:8
<b>Karnofsky</b>	<b>know</b> 18:12	359:5	306:12 312:15	161:20 192:17
160:18,22	27:20 80:5	<b>Koch</b> 2:9 5:7	317:16,17	213:6,11
262:21 266:3,3	86:7,12,19	26:8 118:21	328:20,21,21	221:11 257:4
266:7	93:20 106:14	249:14 250:13	344:17,18	258:14 262:21
<b>Karwoski</b> 4:7	109:19 111:15	250:16,16	352:6,6 353:11	281:20 283:3
10:3,3	117:15 119:3	<b>Kong</b> 268:9	353:12 367:13	307:11 311:12
<b>keep</b> 91:17	122:11 127:5,8	<b>Korvick</b> 4:9	367:14,15	312:1 320:16
107:16 111:14	127:20,21	10:10,10,15	371:5,5 377:22	322:21 328:3
278:1 293:1	128:9 130:14	16:4,10 187:20	378:1	331:14 339:17
304:5,11 311:7	185:19 187:3	193:11 194:6		340:19 351:4
328:18 329:8	189:21 193:19	197:3 198:21	<b>L</b>	364:17 375:14
351:8 361:19	195:8 201:14	211:15 285:3	<b>lab</b> 178:16	382:14 383:20
<b>keeping</b> 44:22	201:15 206:3	305:11 326:6	<b>label</b> 39:12	<b>largely</b> 22:21
<b>keeps</b> 245:4	206:19 207:15	327:13 328:8	44:22 88:21,22	65:10 67:12
<b>Kenneth</b> 2:9 5:9	219:7,22	328:11 367:12	89:19 93:17	69:7 77:17
26:9	221:17 231:7	368:10 369:1	98:8,21,22	110:7 225:2
<b>ketorolac</b>	231:20 232:18	370:7 374:6	99:1 295:3	259:14 268:10
192:10 217:15	235:21 236:5	<b>Kramer</b> 3:3 9:14	363:12 364:14	282:5 310:19
337:10,12	242:9,12 243:1	9:14 94:13,15	<b>labeling</b> 88:18	<b>larger</b> 67:14
349:21 350:2	244:1 255:20	94:15 96:20	89:11 173:10	133:7 140:9
<b>key</b> 37:5 40:3	257:21 259:3	97:7,20,22	174:21 176:5	141:11 142:18
47:22 59:14	260:10,20	98:4 194:13,14	213:21 219:14	217:9 256:18
114:14 122:8	261:5 264:8	195:20 205:4	227:19	313:18
138:14 199:6	277:19 280:4	207:7 220:18	<b>lack</b> 68:9 74:21	<b>largest</b> 39:7
275:15 298:22	286:7,10,15	220:19,19	75:1 99:15	115:9 165:12
333:8	288:10 289:2	233:20,22	<b>ladies</b> 92:3	<b>lastly</b> 167:3
<b>Khuri</b> 82:8	295:13,20	247:14,15,15	118:17 127:17	<b>late</b> 188:21
<b>KI</b> 38:21 117:2	298:1 300:18	248:5,10,13,19	<b>laid</b> 323:8	<b>laws</b> 11:10,13,21
274:15 275:5,6	308:15 309:1	293:13,14	<b>landmark</b>	<b>laxatives</b> 229:12
<b>kick</b> 302:12				

<b>lead</b> 41:13 60:14 221:9 271:9 319:10	<b>letters</b> 176:2	323:15 337:14	379:8,9	<b>location</b> 162:20
<b>leader</b> 10:4,8 134:3,7	<b>letting</b> 355:8	<b>likelihood</b> 71:18 73:2	<b>Lincoff's</b> 226:12	<b>locations</b> 163:4
<b>leading</b> 27:9	<b>let's</b> 8:10 37:11 48:2 100:2	<b>likewise</b> 260:9 283:6	<b>Linda</b> 5:16 20:15,19 26:13	<b>logic</b> 179:19 180:2 376:12
<b>leads</b> 201:17 220:13	102:19 104:10	<b>limit</b> 91:16 271:22 365:2	<b>line</b> 52:20,22 71:21 81:6	<b>London</b> 118:19
<b>leak</b> 105:9,10	114:4,18	377:11	107:7 222:11	<b>long</b> 72:20 130:5 130:9 132:21
<b>leap</b> 350:14	123:19 139:15	<b>limitation</b> 69:3 302:7	249:7 270:3	197:8 261:7
<b>learned</b> 23:15 49:4 358:10	141:3 144:12	<b>limitations</b> 73:5 152:8 177:7	340:7 354:12	275:16 296:2
<b>learning</b> 261:9 262:14	147:3 179:7	302:9	<b>lines</b> 339:12	313:16 317:21
<b>leave</b> 212:9 214:5 227:17	187:22 188:1	<b>limited</b> 11:14 34:13 74:19	<b>link</b> 271:2	318:22 321:22
242:22 286:3	223:11 233:5,7	89:9 116:11	<b>linked</b> 302:1 374:5	323:7 344:4
<b>leaving</b> 128:1 253:10 271:17	254:9 326:19	164:3 165:19	<b>lipid</b> 120:13	353:9 372:20
<b>led</b> 24:7 48:19 74:9 201:12	327:19 330:7,9	173:17 178:4	<b>lipoma</b> 70:8	<b>longer</b> 32:14 39:2 49:9 85:4
254:18	349:12 351:10	185:8 194:21	<b>liquids</b> 40:1 128:7 135:16	107:17 109:4
<b>Lee</b> 5:14 25:12 35:4 94:5	352:17	202:18 204:15	245:8,9 246:15	109:21 113:19
113:8 127:16	<b>level</b> 130:4 140:13 168:14	227:15 259:13	<b>list</b> 18:18 104:21 233:9 322:15	143:15 147:20
233:3 236:9	171:3 176:12	269:20 362:6	<b>listed</b> 142:2 294:4	180:11 181:2
<b>left</b> 7:18 34:10 52:1,21 94:10	177:14 267:10	<b>limiting</b> 86:20 176:17 179:22	<b>literature</b> 82:5	183:10 204:17
96:16 100:18	279:6 344:22	366:17	<b>little</b> 72:2 111:1 111:5 112:5	240:5 241:6,10
151:2 160:3	<b>levels</b> 71:10 76:19 84:4	<b>limits</b> 176:8,19	124:10 131:16	274:16 280:3
212:14 237:12	117:2 140:18	<b>Lin</b> 2:5 9:13 109:1	195:19 197:2	291:21 333:9
240:4 242:14	<b>leveraged</b> 252:16	<b>Lincoff</b> 3:8 9:21 9:21 115:16,17	203:2 205:9	374:14 385:11
281:15 311:14	<b>Levine</b> 3:6 9:5,5 112:3,4 230:8	116:20 117:5	218:4 219:13	<b>longer-term</b> 19:7 201:9
<b>length</b> 32:12,14 41:5,6 43:3,14	230:9,17,22	197:18,19	250:12,15	310:17
46:2 48:15	231:20 232:4	199:5 202:4	260:22 262:19	<b>longest</b> 276:12 320:1
49:3 55:13	232:12,17	222:9,10	286:21 291:8	<b>long-term</b> 61:15 62:7 76:1 77:3
57:22 59:13	286:18 296:16	223:14 228:1	315:14 317:18	77:22 110:2
100:12 101:10	296:17 306:9,9	279:1 281:17	340:20 342:9	155:17 161:14
143:10,22	329:15,15	301:12 306:2,2	343:1 350:13	165:12 195:9
227:4 239:22	341:4,5 351:15	316:1 318:15	355:15 356:4	201:13 203:19
<b>lesions</b> 70:12 71:20	351:15 354:6,7	318:16 329:14	358:21 375:20	204:13,14
<b>lesser</b> 67:21	371:3,3 377:5	329:14 333:4,5	<b>live</b> 333:9	205:6 277:17
<b>letter</b> 23:21 24:8 85:1 136:19	<b>LEWIS</b> 2:3	351:18,18	<b>lived</b> 289:16	279:4,9 310:11
140:21 196:9	<b>LICHTENST...</b> 2:11	362:2,3 364:17	<b>lively</b> 20:9	311:2 313:5,6
196:13	<b>life</b> 338:17 343:5 345:12 368:22	365:18 370:18	<b>liver</b> 178:16	313:14 316:2
	<b>lifetime</b> 314:3	370:18 371:22	<b>lives</b> 255:21 333:20 367:2	319:10,20
	<b>life-saving</b> 327:10	372:1 373:2	<b>localization</b> 259:11	321:15 324:14
	<b>life-threatening</b> 342:14	374:17 375:22	<b>locally</b> 208:13	325:20 336:5
	<b>life-type</b> 344:22	376:1 377:9,12	<b>located</b> 36:19 208:2,4	348:20 352:20
	<b>light</b> 184:5	377:17 378:17		353:2,14

372:19 383:6 385:8,20 <b>long-terms</b> 279:16 <b>look</b> 7:22 18:14 20:9 95:1 96:13 97:1,14 98:15 100:19 101:16,20 102:16 103:13 104:13,20 105:8,19 108:14 110:15 113:6,15,22 114:6 117:14 119:9 123:19 124:7 131:7 132:21 153:22 154:11 162:11 162:15 171:3 173:18 175:7 189:1 197:22 199:9,13,19 200:4 202:7,8 205:17 207:4 214:14 215:11 216:8 217:11 217:13 221:7 227:1 229:8 233:7 234:13 236:21 239:20 240:2 243:2,3 248:15 250:9 254:9 255:4,14 257:19 258:2 265:8 269:7,8 279:14 280:12 283:10 287:21 291:19 294:18 296:11,21 308:18 309:11 313:7,14 314:4 318:2,8 332:1 337:4 344:22 345:8,12 349:7 354:22 356:20 357:13 362:7 362:16,17	367:2,10 <b>looked</b> 82:4 95:6 96:20 102:20 103:2 107:2 109:7 113:10 119:21 120:1 163:9 188:20 192:12 195:12 202:17 215:2 259:3,4 262:5 263:8 266:2 273:20 282:6 283:15 299:21 309:12,13 349:3 <b>looking</b> 32:12 82:18 97:4,5 98:3 106:5 155:18 188:5,7 189:13,15 190:6,10,22 194:8,11 215:6 226:13 239:1 243:4,5,17 250:14 252:6 255:2,11 258:8 265:2,17 269:18 270:17 271:5 277:15 277:17,21 279:9,22 280:2 298:5 310:8 318:13 333:18 334:5 338:22 339:13,15 340:2,6 342:16 345:15 349:13 349:14 356:19 366:7 <b>looks</b> 105:19 131:9 191:8 198:20 299:20 343:8 348:1 358:21 381:5 <b>Los</b> 2:6 <b>lose</b> 380:7 <b>Losing</b> 306:6 <b>lost</b> 151:22	276:1 345:15 <b>lot</b> 122:14 130:14 184:20 194:15 197:14 212:13 260:7 276:11 278:19 280:8 282:1 287:1,14 312:15 316:9 316:11 321:8 321:21 322:11 328:11 332:19 338:12 340:22 341:1 350:2,3 364:2,9 374:9 <b>lots</b> 213:9 286:1 360:17 <b>LOUIS</b> 2:9 <b>love</b> 281:12 335:2 <b>low</b> 50:6 65:7,13 67:4 68:6 75:19 80:2,22 81:3 82:21 96:1 103:6,11 105:17 106:3 107:6 116:16 135:4 157:14 171:7 226:22 227:4 256:13 368:3 375:18 380:10 <b>lower</b> 8:7 13:9 16:19 41:19 42:3 48:21 81:8 103:15 105:1,9,20 106:10 135:9 138:16,19 143:20 145:13 146:2,19 154:4 160:22 284:8 295:18 324:3 326:13 381:18 <b>low-dose</b> 170:22 <b>low-risk</b> 257:2 379:21 <b>lunch</b> 7:8 210:17	210:18 211:4 <b>luncheon</b> 210:22 <b>lung</b> 159:9 160:13,15 265:14 <b>lying</b> 332:3 339:5 <b>Lyles</b> 5:9 26:9 <b>lymphoma</b> 169:2 <hr/> <b>M</b> <hr/> <b>M</b> 3:3 <b>magnesium</b> 230:2 <b>magnitude</b> 46:21 55:20 96:17 249:9 <b>main</b> 41:4 136:1 159:12 253:2 282:13 358:12 364:12 <b>maintain</b> 246:22 <b>maintained</b> 113:19 <b>maintaining</b> 130:8 <b>major</b> 28:13 31:1 41:3 79:12 87:21 111:18 126:20 153:1 167:7 220:9 222:6 247:21 269:10 345:16 382:22 <b>majority</b> 95:18 96:7 117:3 125:13 144:21 151:6 155:8 158:19 163:5 163:16,19 188:16 203:13 217:3 232:9,10 234:15 273:7 298:16 <b>maker</b> 337:11 <b>making</b> 69:4 127:4 182:14	262:11 278:20 305:2 312:11 356:13 <b>male</b> 145:5 171:16 <b>malignancies</b> 71:7 160:7 <b>malignancy</b> 70:21 156:20 <b>malignant</b> 70:18 71:6 82:19 157:21 158:12 <b>manage</b> 31:13 261:13 277:4 358:12 <b>managed</b> 34:19 <b>management</b> 10:4 20:7 21:4 21:15 24:9 25:4,21 29:18 30:16 34:11,13 35:9 36:2 40:11 58:20 60:9 84:22 85:2,6 86:3 87:7 88:17 89:17 90:7 91:13,16 93:7 93:19 108:8 109:16 134:22 135:13 136:20 219:6 279:12 315:7 341:21 352:13 353:13 354:16 357:9 358:8 360:6,19 361:2,4 365:11 369:7,8,11,22 384:17,20,22 <b>mandate</b> 119:9 173:22 <b>mandated</b> 48:18 <b>mandatory</b> 178:6,7 <b>manifestations</b> 34:22 <b>manipulation</b> 193:22
--	--	--	--	--

<b>manner</b> 128:12	144:18 164:19	<b>means</b> 231:7	141:7,21	333:9 345:14
<b>manufacturer</b> 363:15	186:13 195:6	243:3 250:14	142:14 188:6,7	<b>meet</b> 173:5
<b>marathon</b> 347:2	197:1 199:17	251:19,20	189:5,7,11,14	<b>meeting</b> 1:7 6:4
<b>Marc</b> 119:2	206:7 207:3	252:3,5,12,21	190:5 241:1,4	6:11,18 7:7,13
<b>margin</b> 358:11	222:15 223:19	252:22 282:4	241:14,14	8:1,4 11:2,17
<b>marginal</b> 333:19	228:11 239:22	284:20,21	242:21 243:2,5	12:14 13:14
334:14 341:8	240:14 241:1,4	289:3 354:3	243:12 248:8	15:3,8 20:11
384:4	241:12,14	365:22 366:9	248:14,16	24:13 90:9
<b>marginally</b>	243:14,14	369:5	249:6,15,18,20	183:18 348:4
301:11 334:10	248:8,19	<b>measure</b> 34:8	250:4,8,21	359:3 386:1,3
342:4	249:15 250:2,6	41:2 43:12,15	251:16 253:18	<b>meetings</b> 6:15
<b>MARJORIE</b> 4:3	251:21 252:14	73:8 98:3	259:21 285:1	206:12 324:17
<b>Mark</b> 3:16 10:1	252:17 253:2	250:3 284:7	<b>medians</b> 247:19	354:9
92:12	259:20 261:10	332:7 381:17	250:14	<b>member</b> 92:14
<b>marked</b> 90:21	280:15 285:1	<b>measured</b> 54:8	<b>mediated</b> 129:9	<b>members</b> 2:2,16
231:10	287:16 291:9	139:18 143:3	<b>mediators</b> 28:22	3:2 6:12 7:5,9
<b>marker</b> 189:1	291:14,15	143:22 144:4	<b>medical</b> 2:8,20	7:12 8:11 11:6
<b>markers</b> 74:3	292:2,5,8,10	183:16 284:10	3:3,7,13,17	11:18 12:14
<b>market</b> 24:21	292:13,13,15	381:20	4:18 9:6,15	13:15 15:15
91:22 255:22	295:11 299:9	<b>measures</b> 33:21	10:8 25:9 26:4	16:11 20:21
315:2 323:1	311:18 322:9	34:2 40:22	30:18 35:5	26:14 92:7
375:20 377:16	333:8 335:21	43:4 47:18	60:18 85:12	118:21 133:16
<b>marketed</b> 221:3	340:4 343:16	55:21 243:4	134:2,7 140:4	210:20 212:14
<b>marketing</b> 176:8	359:21,21	276:3 343:3,4	148:9 181:20	304:3 327:14
<b>marrow</b> 168:10	367:17,22	345:1 357:10	183:15 269:5	<b>membranes</b>
<b>Maryland</b> 1:20	368:4 372:3	<b>measuring</b>	273:18,18	116:16
<b>matter</b> 240:12	373:5 374:2,16	123:1 335:21	287:7 302:18	<b>memory</b> 326:14
250:9 257:18	380:13	<b>mechanism</b>	338:2	<b>mention</b> 231:5
260:4 270:14	<b>meaning</b> 194:17	35:12,18 36:1	<b>medication</b> 83:6	234:18 251:11
290:11 340:19	243:14 249:10	99:8 112:2	126:16,18	<b>mentioned</b> 31:9
373:20	282:9	195:8 210:3	128:9 129:12	50:21 104:13
<b>matters</b> 262:1	<b>meaningful</b>	269:13 308:6	176:6 177:4	136:16 139:18
<b>mature</b> 263:16	18:21 24:22	<b>mechanisms</b>	221:20 241:7	152:9 153:8
<b>maximum</b> 37:22	41:1 49:16	197:16 220:3	247:4 254:5	156:21 168:20
67:11 138:11	60:11 85:17	316:1 319:5	279:5 314:2,14	207:12 242:20
260:10	90:14 91:1	374:18 385:14	314:16 326:2	262:20 296:11
<b>Mayo</b> 3:13 9:11	144:8 190:12	<b>mechanistic</b>	345:5,19	342:13 347:20
297:20	235:6,11,13	302:5 322:12	346:22 347:5	359:13 365:4
<b>mean</b> 46:22 47:9	238:10 251:10	<b>mechanistically</b>	<b>medications</b>	377:10
47:17 49:22	251:12 285:5,7	320:11 321:19	75:17 229:8,9	<b>metabolism</b> 75:5
50:13 53:10	285:10,14,19	321:20	229:10	77:3 110:2
54:10 56:1,17	293:5 295:5	<b>media</b> 7:10,14	<b>medication-re...</b>	166:13
57:7,22 59:13	301:10,14	7:15	174:4	<b>metabolite</b> 36:7
63:4 98:17	302:19 304:17	<b>median</b> 47:1,5	<b>medicine</b> 2:9,10	36:7,10 84:1,4
101:10 105:7	305:14 308:1	47:16 50:13	2:13,21 3:8 6:5	135:7 166:20
107:16 109:15	382:8	53:13 54:12	6:7 26:17	168:22 169:5,9
121:8 143:10	<b>meaningfulness</b>	56:18 57:10	277:18 279:11	172:9 311:20
	70:16 335:21	98:17 140:1,5	303:10 318:4	311:22

<b>metabolized</b> 36:6	<b>micromolar</b> 167:12,17	230:15 236:12 272:11 293:1	265:18 302:14	<b>morbidity</b> 21:9 41:13 84:15
<b>metastases</b> 267:1	<b>micronucleus</b> 169:3,8	311:8 334:1 339:14 347:18	<b>modeling</b> 303:5	132:16 152:11 345:16
<b>metastatic</b> 161:5 266:20	<b>microphone</b> 8:16 92:10	<b>minds</b> 286:10	<b>modest</b> 71:9 220:16 232:5	<b>morbidity/mo...</b> 346:4
<b>meta-analysis</b> 34:1	263:7 297:14	<b>minimal</b> 186:10 218:18 272:2	256:20 333:19 341:8	<b>moribund</b> 266:10
<b>methadone</b> 361:21	<b>middle</b> 249:8	284:9	<b>modified</b> 46:9 89:12 216:12	<b>morning</b> 6:3,10 9:18 10:19
<b>method</b> 47:8 185:18 366:17	<b>midnight</b> 289:1 289:5	<b>Minimally</b> 2:19	<b>molecular</b> 135:1	20:19 35:4,22 37:4 60:18,19
<b>methodologic</b> 283:7	<b>mid-dose</b> 170:22 171:8	<b>Minimization</b> 172:21 173:4	<b>molecule</b> 116:15	61:7 118:16,17 125:12 128:2
<b>methodologic...</b> 368:2	<b>mightily</b> 338:14	<b>minimize</b> 33:8 85:4 177:20	<b>moment</b> 331:20	134:6 148:13 165:22 211:16
<b>methodology</b> 94:8 201:1 368:5	<b>mike</b> 9:1 377:6	<b>minimized</b> 179:21 181:22	<b>Monday</b> 300:20 340:13	212:22 289:9 289:17,22
<b>methods</b> 364:11	<b>milestone</b> 55:12	<b>minimizing</b> 173:6 294:10	<b>money</b> 239:10 288:7 301:4,6	<b>morphine</b> 36:18 36:22 63:6
<b>metocloprami...</b> 135:22	<b>milestones</b> 44:20 59:14	<b>minimum</b> 18:20 144:2 334:20	312:12 350:5 367:11	96:8,12 99:14 107:16,21
<b>metoprolami...</b> 229:12	<b>militant</b> 71:15	381:19	<b>monitor</b> 31:14 88:5 355:5,12	207:15 209:11 209:17
<b>metric</b> 33:16	<b>milligram</b> 62:13 62:18 63:22	<b>Minnesota</b> 9:12	383:14 385:15	<b>morphine's</b> 209:21
<b>metrics</b> 179:16 183:3	<b>milligrams</b> 23:2 23:11 35:9	<b>minor</b> 12:19 71:3	<b>monitored</b> 174:1 353:9	<b>morphine-ind...</b> 209:12,13
<b>metropolitan</b> 290:21	38:15 39:3,6 52:21 54:20	71:3	<b>monitoring</b> 31:18 38:4,11	<b>mortality</b> 32:19 41:13 73:3
<b>MI</b> 225:1,11 228:3,4 256:4	58:14 59:8 60:8 62:19	<b>minute</b> 134:13 253:11	68:12 69:16 76:8 77:15	145:8 152:12 278:5 345:16
257:12 277:21 279:2,20	63:5 76:16 78:21 79:6,8	<b>minutes</b> 133:14 239:14 284:3	84:6 173:22 174:5,8,18	345:18
280:20 308:2 309:11 320:7,9	84:8,18 86:3,9 112:22 113:1,7	293:2 330:10 381:7	336:8 348:20 353:2 356:20	<b>Mortensen</b> 5:10 25:16 60:22
320:14 344:11	140:12,12 147:19 167:19	<b>MIs</b> 154:10 309:3	371:18 385:7 385:12	61:4,5 78:9 111:7 228:7,7
<b>mice</b> 166:18 167:2 169:11	168:4,16,17 169:13,15,22	<b>miserable</b> 346:15 347:22	<b>monitors</b> 83:16 273:15	230:14,20 231:2 232:1,7
169:14 170:3,9 170:13 171:11	170:7 184:17 184:21,22	<b>missed</b> 187:11	<b>month</b> 205:22 284:14	232:14,22 234:9,12,12
171:16,22 172:11 209:10	185:4,5,6,9,10 185:10 186:3,6	<b>missing</b> 322:11	158:14,15,16 158:19 163:12	264:4,4 283:1
209:10	186:8,11,21 187:3,5 209:8	<b>misunderstan...</b> 132:5 253:13	270:14 279:3 279:19 282:7	<b>Mortensen's</b> 110:8
<b>Michael</b> 2:7 3:8 3:10 9:21	209:20 272:6 279:8,11	<b>mitigate</b> 37:18 130:8 275:22	282:14,17,19 320:15,21,22	<b>motility</b> 21:21 27:14 29:4,14
<b>Michigan</b> 26:16 26:19 213:20	341:13,13	<b>mitigates</b> 21:20	372:20	37:2 42:6 99:12 129:5,7
<b>microflora</b> 36:7	<b>million</b> 367:2	<b>MITT</b> 46:15	<b>morbidity</b> 30:13	
	<b>Mimi</b> 4:14 6:8 9:16	<b>mix</b> 227:2		
	<b>mind</b> 111:15	<b>mixed</b> 22:21 320:7		
		<b>mixing</b> 320:6		
		<b>mobile</b> 257:21		
		<b>model</b> 46:19 47:7 180:2		

130:6 214:13	<b>muscle</b> 29:13	<b>narcotics</b> 108:16	<b>neck</b> 160:8	157:12 158:4
<b>motivation</b>	207:12	217:17 220:16	<b>need</b> 12:4 15:20	158:12 159:6
380:1,3	<b>mutagenicity</b>	221:15 222:6	21:12 24:21	235:19
<b>mouse</b> 169:2,3,7	76:13	277:5 375:9	25:9 31:13	<b>neoplastic</b>
169:18	<b>mu-opioid</b> 21:19	376:13	41:18 85:13	268:19
<b>move</b> 19:1 55:8	29:10 36:5	<b>narcotic-indu...</b>	87:9 90:9	<b>neoplasms</b> 137:4
139:15 144:12	37:8 38:21	194:3 215:18	116:12 182:22	147:13 148:15
147:3 152:21	94:18 207:10	219:18,19	183:8 194:1	156:17,17,19
156:16 159:10	208:14 215:20	276:10 277:1	195:4 211:11	157:5,6,11,17
227:7 252:8	235:22 236:5	<b>narcotic-spari...</b>	235:7 249:1	157:18,21
277:12 283:17	274:15 308:7	192:11	271:22 275:9	158:2,9,18,21
283:18 292:6	<b>mu-receptor</b>	<b>narratives</b>	277:16 278:12	159:7,14
292:22 307:5	259:16	202:18	280:2,9 284:3	165:16
324:6 325:10	<b>mu-receptors</b>	<b>narrow</b> 138:1	284:14,17	<b>neoplastic</b> 71:12
325:12 327:11	207:18 259:12	<b>narrower</b> 298:5	304:5 318:1	72:5 169:16
330:3,12 331:9	269:17	<b>narrowly</b> 354:4	330:6 340:7	307:14 310:8
352:9 371:15	<b>myocardial</b> 64:8	<b>nasogastric</b> 33:4	355:14 357:13	324:21 328:6
<b>moved</b> 203:1	65:11,17 66:9	39:19 41:10	359:11,12,17	331:6 383:9
<b>movement</b> 42:5	66:21 68:2	58:11 90:20	359:18 360:21	<b>nervous</b> 28:16
42:17 52:14	80:11 82:6,10	121:15 122:6	362:3 367:19	29:11 36:20
101:1 122:19	88:19 110:11	126:18 127:22	370:3 374:13	166:9 208:9
123:4,17	119:7 120:3	<b>national</b> 3:11,15	380:17 383:13	<b>networks</b> 367:1
138:20 147:7	132:10 150:3	8:18 9:1	<b>needed</b> 33:17	<b>neurogenic</b>
245:17 246:6	198:6 224:12	213:22	47:20 179:3	28:15
247:3	228:10 234:15	<b>nature</b> 173:13	183:4 196:5	<b>neurology</b> 81:15
<b>movements</b>	256:14,22	173:14 190:3	253:11,16	<b>neuroma</b> 70:8
244:18	257:9 282:15	<b>nausea</b> 28:5 31:5	254:3 337:17	<b>neurons</b> 29:12
<b>moves</b> 339:17	316:2	51:11 79:14,15	337:22	<b>neuropeptides</b>
<b>moving</b> 100:6	<b>M.D</b> 2:3,5,7,9,11	135:17 278:7	<b>needs</b> 95:11	28:18
289:20 330:9	2:13,18 3:3,4,6	301:18 342:17	360:4,6 361:16	<b>Neurovisceral</b>
<b>mu</b> 36:21	3:8,12,14,16	342:18 345:2,7	<b>negative</b> 37:1	2:5
<b>mud</b> 313:1	3:19 4:3,5,9,16	345:11 346:19	75:2 76:10,14	<b>nevertheless</b>
<b>multifactorial</b>	4:18,19 5:3,4,6	<b>NDA</b> 22:19	98:8,14 169:4	215:22 222:21
220:10 275:15	5:9,10,13	23:12 136:8	169:9 170:10	287:5 383:8
<b>multimodal</b>		137:7,22	172:10,12	<b>new</b> 3:6 9:6 13:7
32:22 39:16	<b>N</b>	196:15	281:8 297:13	21:4 135:1
<b>multiple</b> 124:6	<b>N</b> 6:1 191:8,9,22	<b>NDC</b> 87:17	297:17	224:13 225:5
124:10 127:8	211:1,1,1	<b>nearly</b> 32:13,16	<b>negatives</b> 342:5	225:11 263:21
129:11 133:10	<b>name</b> 8:12 21:17	78:15	<b>negligible</b> 84:4	268:8 290:11
150:11 162:6	26:14 118:17	<b>necessarily</b>	<b>negotiated</b> 98:21	<b>newer</b> 294:3
239:18 240:21	134:6 234:10	226:6 282:20	<b>neoplasia</b> 64:10	<b>NG</b> 31:6,14
367:4	305:18 306:18	315:9 324:19	76:20 77:2	41:14 58:16
<b>multivariable</b>	328:19 329:8	334:19	82:19,20 157:3	60:6 125:2,11
95:1	351:9,22	<b>necessary</b> 12:11	157:13 161:11	125:13,16
<b>multi-event</b>	370:14 371:9	186:12,15	161:13 353:5	126:2,8,13
264:6	<b>narcotic</b> 108:10	354:12 368:14	<b>neoplastic</b> 382:17	127:3,7 301:18
<b>multi-variant</b>	220:8,15	369:7,11,17	<b>neoplasm</b> 69:21	338:16 345:3
265:17	361:20	385:1,13	70:6,18 71:16	346:14 347:21

349:7	216:19,22	73:7 100:5	234:21 253:11	63:16,21 67:9
<b>nice</b> 238:15	217:10 301:12	154:3,9 155:12	253:16 254:3	67:19 68:18
<b>night</b> 302:11	<b>non-gut</b> 213:8	180:9 181:19	265:13 266:20	69:13 71:22
<b>nine</b> 34:9 143:16	<b>non-ischemic</b>	201:8 234:18	266:22 268:4	72:6,13 74:17
240:15 255:9	69:2,10 150:7	265:12	282:7 283:3	74:20 75:9
255:17 317:4	153:19 154:7	<b>noted</b> 15:11,22	287:18 303:6	76:2 77:8,10
352:7	154:17 200:16	17:15 64:2	308:9 337:17	77:21 78:3
<b>Ninety-four</b>	<b>non-mortal</b>	65:20 80:19	337:22 350:12	82:15 91:7,8
46:13	198:6	84:12 228:13	364:17 375:21	110:6 111:7
<b>NK</b> 269:22	<b>non-opioid</b>	354:11	<b>numbers</b> 47:20	117:7,19
<b>NNT</b> 33:17,18	36:14 48:18,21	<b>notice</b> 103:4	70:4 81:21	118:11 122:1
34:4,6 47:21	<b>non-opioid-in...</b>	204:4	111:6 175:9	131:5 132:16
58:18	294:19	<b>noticed</b> 159:16	202:2 213:17	134:18 136:15
<b>NNTs</b> 55:6	<b>non-POI</b> 102:3	160:5,16	213:22 214:18	137:5 147:4,5
57:19 59:21	<b>non-small</b>	307:15	223:3 225:8	147:8,14,16,17
254:11 255:6	160:12,15	<b>noting</b> 79:4	249:7 256:18	147:21 148:2
255:16	265:14	231:4	258:14 265:7	148:19,22
<b>NOAEL</b> 168:14	<b>non-United</b>	<b>notoriously</b>	298:18 303:7	149:3 152:22
<b>nonclinical</b>	232:13	362:6	324:13 333:18	153:1,14
166:1,2,4	<b>non-U.S</b> 42:22	<b>novel</b> 21:3	349:13,14	154:11 155:21
167:7 172:2	45:22 48:4	<b>November</b> 84:22	350:14 375:18	156:3,7,13
<b>nonfatal</b> 146:20	218:12 230:22	136:17,18	<b>numeric</b> 73:16	157:10,14
<b>non-adjudicat...</b>	<b>non-voting</b> 3:18	359:6	156:5 266:21	159:10,12
117:13 198:2	4:2 284:1	<b>nowadays</b>	320:3	161:9,19
198:16,22	307:6 371:17	127:19,21	<b>numerical</b> 65:9	162:10,12
200:1,3,14,15	381:14	<b>NSAID</b> 220:11	80:10 88:18	164:18,22
201:4 222:20	<b>North</b> 5:8 26:8	<b>NSQIP</b> 82:8	91:6 119:6	165:13 204:6
<b>non-approved</b>	39:7 42:21	366:8	157:15 224:22	223:16,18
88:9	44:6 46:1,5,14	<b>NULL</b> 71:10	232:18 265:12	224:2 257:8,10
<b>non-cancer</b>	48:6,13,16	72:1 75:20	<b>numerically</b>	257:13 263:1
63:20 67:10,19	49:2,10,18	<b>number</b> 33:17	51:10 145:13	282:3 308:17
71:22 72:6	50:18,19 52:13	39:8 67:3	146:2 321:2	309:1,17,22
74:18 153:3,7	56:8,14 58:5	69:20 71:8,17	<b>nurse</b> 288:21	311:7 319:22
153:9,14	59:2 60:1,4	73:15 98:18,20	<b>nurses</b> 340:12	320:17 343:17
154:12 157:11	83:15 142:20	102:13,14	340:15	373:10,17,18
157:14 159:8	143:11 192:19	115:9 121:22	<b>nursing</b> 31:13	377:1
161:9,15	193:5 250:17	122:20 126:2	33:2 56:13	<b>OBDs</b> 324:14
162:13 204:6,7	258:8	128:18 133:5	181:8 361:21	<b>obesity</b> 149:10
204:9,11,16	<b>Northwestern</b>	138:11 149:12	<b>nutrition</b> 135:19	<b>objection</b> 186:5
326:18,20	2:4 6:6	149:16 153:12	<b>nutritional</b>	187:1
<b>non-clinical</b>	<b>nos</b> 307:2	155:12 157:17	31:17 238:1	<b>objective</b> 30:20
134:21 259:10	<b>nosocomial</b>	157:20 159:4	<hr/>	122:22 139:5
<b>non-clinician</b>	30:14 101:22	164:2 176:20	<b>O</b>	174:16 186:1
260:17 296:3	102:18 106:11	191:10 199:14	<b>O</b> 6:1 211:1,1,1	264:15 299:11
<b>non-event</b> 252:1	271:18 278:6	199:20 222:19	<b>OBD</b> 22:14 24:6	302:1 343:8
<b>Non-fatal</b>	345:20	224:20 225:16	25:18 61:2,10	<b>objectively</b>
145:12	<b>notable</b> 172:6	231:16,21	61:20,22 62:9	139:6 185:17
<b>non-GI</b> 216:14	<b>note</b> 16:6 64:15	232:4,5,7,18	62:15,17,21	<b>objectives</b> 44:15

173:6,9 174:10 174:22 179:14 183:1 <b>objectivity</b> 198:7 <b>observation</b> 47:14 52:19 53:12 66:13,22 74:12 84:2 96:18 132:6 180:8 201:18 242:13 243:16 <b>observational</b> 322:21 363:8 <b>observations</b> 69:14 77:20 132:15 <b>observed</b> 54:4 54:18 55:22 57:4 61:12 66:2,5,7 69:1 69:19 72:5 82:10 91:2,6 157:16 161:16 168:13 171:11 312:1,2 <b>obstruction</b> 40:17 80:4 145:17 314:12 <b>obtain</b> 203:21 249:4 <b>obtained</b> 14:20 47:10 191:9 <b>obvious</b> 213:4 232:21 <b>obviously</b> 128:10 238:14 257:21 268:14 268:18 281:13 299:14 314:8 314:18 319:3 319:12 331:7 336:2 337:2 <b>OC</b> 223:17 <b>occur</b> 42:1,4,15 56:10 89:8 125:13 155:1,4 155:9 160:14	231:8 247:11 <b>occurred</b> 54:13 65:18,21 66:11 91:9 123:12,16 123:16 131:5 132:11 149:22 151:13 152:17 158:15,16,18 158:19 159:1 159:17,19 163:5,13 180:7 228:10,13 273:12 274:1,4 281:3 283:9,12 335:7 <b>occurrence</b> 43:17 91:11 150:17,20 246:6 <b>occurring</b> 52:15 79:19 131:10 154:19 <b>occurs</b> 27:6 <b>odds</b> 222:21 309:7,20 <b>offer</b> 282:2 <b>offered</b> 40:1 <b>offers</b> 27:21 <b>office</b> 3:10,20 4:7,11 10:4,6 10:12 14:22 273:18 <b>officer</b> 60:19 <b>official</b> 4:13 9:17 15:4 206:13,14 327:19 <b>off-label</b> 85:5 135:21 192:10 213:11,12 214:5 297:5 354:2 355:6 357:18 361:13 361:18 365:6 380:21 381:3 385:4 <b>off-target</b> 36:16 <b>OG</b> 125:16 <b>oh</b> 192:1 195:16	290:4 305:15 324:6 356:3 <b>okay</b> 20:14 101:13 125:15 134:13 183:17 184:9 190:11 190:16 191:19 211:3 232:22 242:22 244:19 245:1 274:17 274:18 275:2 281:21 292:6 330:7 367:12 369:14 370:6 377:5 <b>okayed</b> 182:19 <b>old</b> 144:19,20 <b>older</b> 51:18 144:20 164:15 <b>once</b> 37:1 68:3 92:18 125:18 150:9 153:18 160:1 163:7 191:22 192:5 196:22 244:18 244:22 289:17 289:18 296:3 314:3 316:3,15 357:19 359:13 <b>oncologist</b> 26:7 269:5 <b>oncologists</b> 71:2 268:22 <b>oncology</b> 3:13 266:5 267:13 338:2 <b>one-day</b> 260:12 <b>one-third</b> 319:21 320:1 320:16 <b>ongoing</b> 119:4,5 136:15 <b>onset</b> 225:5,11 274:5 <b>on-label</b> 256:1 362:10 <b>open</b> 6:18 7:7 8:3 27:5 92:5	183:18 211:6 214:3 227:3,16 298:7,17 378:20 <b>operated</b> 203:14 <b>operates</b> 358:11 <b>operation</b> 106:13 227:5 285:11 303:17 313:22 314:7 314:11 356:2 <b>operational</b> 183:4 <b>operations</b> 92:22 221:9,14 286:8 347:17 <b>opiate</b> 62:9 209:2 210:7,13 213:9 269:14 269:19 361:15 384:2 <b>opiates</b> 153:3,4 269:19,21 <b>opiate-induced</b> 119:10 <b>opinion</b> 19:19 185:22 295:4 350:16 383:11 <b>opinions</b> 6:16 <b>opioid</b> 22:13 24:6 29:7 36:17,19 37:5 40:12,19 46:2 48:14 49:1 59:4 61:13,19 63:2,4,12,14 72:9,12 75:15 77:4 84:13 95:7,11 96:7,8 97:5,6 98:9 99:20 107:14 107:21 109:4,9 110:1,2 116:3 130:4,5,10 164:19 205:20 208:2,3 218:3 218:13 219:1 226:7 233:7	235:22 293:21 300:1 336:19 357:16 <b>opioids</b> 21:20 29:9 33:8 37:2 37:19 40:17 62:4,8 86:6 89:4 94:21 99:11,19 109:14,21 137:18 147:9 218:16,19 233:13 235:21 275:15,17,20 275:22 294:11 336:14,17 <b>opioid-based</b> 29:16,20 40:10 48:17,22 58:22 95:20 <b>opioid-induced</b> 19:7,14 61:11 147:4 148:18 294:19 <b>opioid-receptor</b> 75:4 135:3 <b>opioid-sparing</b> 33:7 97:8,12 218:13 294:5 335:6 349:22 <b>opioid-tolerant</b> 86:8 89:8 <b>opportunity</b> 100:11 101:19 238:18 240:16 374:10 376:21 <b>opposed</b> 43:16 62:18 122:18 159:21 281:7 291:22 <b>optimal</b> 38:16 <b>optimum</b> 30:8 <b>option</b> 85:14 87:18 <b>options</b> 32:21 34:13 85:22 315:1,8 322:13 322:15
---	--	---	---	---

<b>oral</b> 27:16 135:4 167:20 168:18 169:10 208:22 246:21 <b>orally</b> 128:9,10 <b>orange</b> 52:20 <b>order</b> 6:4 18:6 34:7 37:17 39:17 41:15 43:7,13,16 49:7 56:7 57:21 97:22 114:17 128:18 139:14 142:5 143:4 188:8 229:2 239:21 240:10 241:19 241:22 243:19 249:4,9,22 254:5,8,10 276:4 293:7 294:8 299:2 300:14,21 364:22 367:1 369:13 <b>ordered</b> 182:18 <b>ordering</b> 87:18 <b>orders</b> 56:12,16 57:15 242:4 256:18 299:13 <b>organ</b> 168:7 170:15 172:7 <b>organs</b> 207:19 210:15 <b>oriented</b> 385:3 <b>origin</b> 224:16 <b>original</b> 136:8 137:22 158:4 211:5 <b>originally</b> 18:1 274:14 331:1 368:19 <b>orthopedic</b> 213:9 347:12 376:17 <b>orthopedist</b> 365:5 <b>oscillation</b> 225:9	<b>osteo</b> 355:3 <b>osteoma</b> 170:8 170:19 <b>osteopenia</b> 75:17 <b>osteoporotic</b> 163:8 165:1 <b>osteoporotic-t...</b> 162:22 <b>osteosarcoma</b> 170:9,20 <b>ostriches</b> 367:8 <b>outcome</b> 18:1,14 18:22 34:8 48:11 121:6 174:13 175:10 203:20 265:22 266:9,19 293:9 318:14 333:1 343:6 <b>outcomes</b> 46:8 59:22 175:7,8 175:13 181:21 183:15 192:16 216:12 267:14 375:17 <b>outlier</b> 241:15 <b>outliers</b> 188:14 248:20,21 252:16 <b>outline</b> 25:12 84:21 179:12 179:13,18 180:13 365:13 <b>outlined</b> 322:16 365:19 <b>outpatient</b> 17:4 22:14 45:16 90:4 148:3 180:20,21 181:3,16 183:9 357:11 363:18 <b>outpatients</b> 181:11 <b>outreach</b> 175:2 175:19,22 <b>outside</b> 48:5 85:9 86:5,17	88:2 180:7 209:3 <b>outweigh</b> 303:9 331:12 334:1 334:21 344:15 351:2 383:18 <b>outweighs</b> 12:5 342:1 351:7 <b>ovary</b> 169:7 <b>overall</b> 29:22 37:13 48:22 55:13 68:6 74:5 76:21 80:2 112:18 144:18 150:15 165:11 215:5 218:3 232:10 268:2 291:14 292:2,13,15 331:11 332:13 333:1 338:4 339:11,22 346:7 351:1 378:8 383:17 <b>overcome</b> 342:4 <b>overlap</b> 77:11 132:12 <b>overlaps</b> 67:12 <b>overly</b> 87:2 <b>override</b> 181:18 <b>overseas</b> 192:13 <b>oversight</b> 69:17 <b>overused</b> 302:22 35:12,20 <b>overwhelming</b> 163:16 <b>owe</b> 354:22 <b>owing</b> 68:5	185:12 <b>packaged</b> 177:7 <b>packages</b> 17:16 <b>packaging</b> 89:12 177:2,2,3,3,5 180:18 <b>packet</b> 199:12 247:21 <b>page</b> 199:12 <b>pager</b> 7:21 <b>paid</b> 239:14 377:15,16,17 <b>pain</b> 28:8 29:18 40:11 58:20 59:5 60:9 61:18 62:2,22 63:10,20 67:10 67:19 72:8,12 108:8 118:22 135:18 147:9 153:3,4,11 159:13 219:6 277:5 303:18 346:13 <b>painful</b> 303:17 <b>pairwise</b> 169:20 170:5 <b>palliative</b> 72:22 <b>panel</b> 268:21 314:21 324:16 384:19 <b>panels</b> 287:4 <b>PANKAJ</b> 2:13 <b>panoply</b> 270:17 <b>paper</b> 82:8 112:15 349:2 <b>paperwork</b> 340:16 <b>parameter</b> 188:9 <b>parameters</b> 167:16,22 <b>Pardon</b> 297:16 <b>parent</b> 116:17 311:21 <b>parenteral</b> 29:8 <b>parenterally</b> 130:10	<b>parking</b> 348:3 <b>Parklawn</b> 15:1 <b>part</b> 15:4 18:10 92:21 93:22 94:6 100:3,5 103:6 113:11 120:16,17,18 127:13 129:19 129:22 208:2 236:10,11 237:5,6 268:13 281:13 285:14 322:9 361:2 383:5 <b>partial</b> 8:8 13:10 16:20 40:5 45:2 135:10 137:13 307:11 328:3 331:14 382:14 <b>participant</b> 15:18 <b>participants</b> 2:1 3:1 4:1 5:1 11:17 15:20 16:1 <b>participate</b> 14:15 174:3 <b>participating</b> 15:7 200:22 <b>participation</b> 8:2 <b>particular</b> 12:4 61:3 68:1 106:7 156:19 177:20 208:6 209:19 243:9 243:20 250:20 251:4 296:7 298:6 302:4 308:2 309:7 310:22 325:8 361:6 374:19 374:21 <b>particularly</b> 29:8,19 39:6 99:15 103:13 111:21 120:10
<b>P</b>				
<b>P</b> 2:21 6:1 46:20 112:11 140:13 141:13 170:17 171:3 <b>package</b> 17:10 92:17 176:6 177:4 184:18				

130:10 133:8	33:1,3 294:1	22:1 23:1 24:2	131:3,12	232:8,9 233:11
198:5 216:5	<b>patient</b> 2:17 9:9	24:6 25:1 27:6	132:22 137:12	233:16 234:2,6
217:19 231:10	17:19 21:8	27:11 31:4	137:17 143:13	234:22 235:7
240:5,17	29:22 30:6	32:13,18 33:22	143:14 144:14	235:16 236:3
301:16 325:8	31:11,20 32:7	34:3,20 37:16	144:15,20,22	236:21 237:5
327:9 337:9	33:6 34:17	38:7 39:1,8	145:3,4 146:1	237:17,21
355:2 372:8	38:1 41:8,11	40:4,9,14	146:13 147:7	240:5,9,13,15
<b>parties</b> 337:1	44:7,21 51:15	42:13 44:19	149:9,13,15,17	241:5,10 242:9
<b>partly</b> 246:10	55:8 66:17	45:2,5,6,13,15	151:2,6,9,11	242:16 244:9
<b>parts</b> 98:12	77:8 100:13	45:20 46:10,14	151:14,15,16	245:4,7,8,11
122:4 356:11	106:9 127:11	49:10 50:5,19	151:20,22	245:15 246:2
<b>Pasricha</b> 2:13	138:5 140:4,6	51:1,4,13,17	152:1 153:2,4	246:14 247:11
9:3,3 99:4,5,6	141:6,9,20	52:12 53:1,6	153:13,15,17	248:4 249:1,4
101:14 104:2,6	142:1,13,15	53:18 55:2,5,7	154:1,3 155:13	254:3,14 255:1
104:9 188:2,3	152:4 155:20	55:14 57:13,16	155:16 157:18	255:7,22 256:3
203:11,12	156:1 162:2,5	59:9,16 60:11	157:19 158:13	256:18 257:21
216:9,10,20	162:6 176:5,6	61:12,17,22	158:22 159:11	258:16 260:2
217:8 258:17	177:4 185:20	62:8,9,16,21	160:3,14,21	261:14 262:7
258:18 262:16	192:4 204:16	63:10,13,16,20	161:10,15	263:20 264:20
262:17 263:10	221:21 238:3	63:21 65:18	162:18,19	265:13,19,22
263:19 284:16	240:4,17 241:4	66:4 67:10,15	165:3,18	266:17,22
284:17 285:8	244:18 253:8	71:19 72:8,11	173:17,21	267:6,19,22
292:8 294:16	253:15,19	72:14,18 73:1	174:3,19	268:2,4,8,15
294:17 306:10	254:5 256:9,11	73:4,5,9,17	175:22 176:4	273:4,8 274:18
306:10 314:19	260:3 263:13	74:8,10 78:15	178:13 181:11	274:19 276:11
314:20 322:7	264:16 266:4	78:18,22 79:5	187:12 188:14	278:18 281:10
325:11,13	266:10 275:16	79:7 80:15	188:16,21	281:19 282:7
326:8 329:1,1	275:20 276:5	82:13,16 83:4	189:2,19 191:6	286:1 287:22
342:6,7 351:14	278:16 285:10	83:12,18 84:18	191:7,10,20	288:17 291:14
351:14 353:20	286:11,12	85:14,18 86:5	192:2,18	299:1 308:10
353:21 371:4,4	288:6 289:1,6	86:8 87:5 89:3	193:20 195:1	311:13,16
373:22 374:1	290:19 291:11	89:8,17 90:2	196:5,22	312:1,2,13,18
378:22	296:12 300:4,6	90:16,20 93:5	197:11,14	312:20 313:15
<b>passage</b> 28:5	300:18 301:3	93:10,20 95:18	201:22 202:8	313:22 314:8,9
42:9	307:10 314:4	95:22 96:1,7	203:14,17,20	314:9,14 315:5
<b>passing</b> 247:2	317:6 321:11	96:10,11 97:11	204:12 205:9	319:22 320:2
<b>passive</b> 311:8	333:15 336:6	97:17 98:9	206:1,22	320:17,19
323:1	336:16 338:1	100:8,16 101:8	207:16 212:2	322:19 323:22
<b>passively</b> 372:6	338:12,15	106:21 108:4	213:18 214:4	328:2 331:13
<b>patents</b> 13:3	339:3,20	108:17,20	214:10,18	332:9,19
<b>path</b> 261:16	340:22 341:15	109:7,10 110:1	215:2,22	333:17 334:22
<b>pathophysiolo...</b>	342:1 346:11	110:6,12 111:2	216:13,17,21	336:8 337:4
99:18 319:12	347:20 348:11	111:8,15,20	217:4,16 218:4	338:1,5,8
<b>pathway</b> 39:16	356:17 360:20	115:9 117:3	219:6 220:8,15	341:17,19
60:3 91:3	361:6 365:2	121:22 122:15	222:5 224:6,20	342:16,19
101:9 239:2	367:2 378:6	125:2,5,10	225:4 226:3	343:10 351:4
335:5,6	379:20	126:10,21	227:16 228:3	355:15,17
<b>pathways</b> 31:1	<b>patients</b> 17:21	128:7 130:2	228:14 230:3	356:8 358:4

360:17 361:15	247:7,10	227:2 256:16	<b>performed</b> 27:2	<b>persisted</b> 157:22
361:21 362:10	260:10 278:11	256:21 267:22	27:4 40:8 52:1	<b>persistent</b> 67:21
362:14 364:18	279:6,8 280:8	268:1,5,8	<b>period</b> 38:11	<b>person</b> 205:8,12
371:19 372:11	281:6 282:13	314:6,11	47:14 52:19	206:16 373:3,4
375:7,21	290:15,16	325:18 326:21	53:12 55:9	<b>personal</b> 15:19
376:16 380:10	291:6,16,18,20	338:3 349:7,9	66:8 67:13	185:22 190:15
382:14 383:19	302:11,12	349:10,11	77:11 91:9	<b>personally</b> 193:7
384:1 385:7,18	316:4 318:9,10	<b>percentage</b>	96:19 100:20	303:16 363:3
<b>patient's</b> 28:1	323:21 333:9	122:5 125:1	100:20 101:5	366:16
29:15 192:6	338:22 345:9	149:9 150:11	110:10 113:19	<b>perspective</b>
238:13 246:20	345:13 350:2,4	157:18 160:21	130:3 131:4	25:11 26:20
262:2 266:9	354:22 355:19	164:14 225:3	132:14 136:13	29:15 33:15
289:7,20	356:1 363:11	240:9 254:22	155:8 174:2	48:10 104:1
332:12,21	368:2 378:3,12	311:13 312:2	177:1 180:8	111:22 113:4
342:3	378:20	332:12	196:15 201:19	113:17 116:12
<b>patient-contro...</b>	<b>perceived</b> 71:14	<b>percentages</b>	212:12 236:22	218:8 236:16
29:16 40:10	<b>percent</b> 27:4	121:17 125:19	237:3,9 242:14	237:20 238:7
293:21	38:22 45:6	<b>percentile</b> 47:1,5	243:7,16 246:2	243:13 244:5,6
<b>patient-level</b>	46:13 48:20,21	47:16 50:16	262:4 274:2	245:21 249:13
81:17	50:4,20 51:2,2	53:14 54:13	275:4 279:15	249:15 250:12
<b>pattern</b> 52:11	51:17,18,21	56:5,20 57:11	280:3 313:17	262:1,2 274:7
56:7 76:22	55:4 56:15	59:16 140:1,2	313:18 316:6	349:12
241:21 242:3,4	57:17 58:18	140:8 141:10	316:19 320:21	<b>perspectively</b>
270:22	59:9 60:7 79:1	142:17 188:6	<b>periodic</b> 174:18	74:22
<b>patterns</b> 49:12	79:3,20 81:3	188:11 189:12	<b>perioperative</b>	<b>perspectives</b>
56:12	83:4,9,12	189:15 190:2,6	51:20 243:6	38:18 113:15
<b>pay</b> 239:6	88:14 96:9	190:10 235:9	256:14	<b>persuaded</b>
<b>payoff</b> 380:1	110:10 111:8	237:15 241:1,3	<b>peripheral</b> 95:2	343:17,18,20
<b>PCA</b> 29:20	121:16 125:1,4	241:9,12	116:3,9 210:3	<b>pertains</b> 103:17
48:17,22 58:22	126:1,3,5,6	248:20 250:4	210:7,13	<b>Pfeffer</b> 119:2
95:20 96:8	131:4 135:5	251:15,16,17	<b>peripherally</b>	<b>Phan</b> 4:14 6:8
98:6,10 193:21	144:19,21	253:15 254:6	21:18 36:11	6:10 9:16,16
233:12 276:14	145:10,11,14	260:14 284:18	37:7	10:17,19 304:6
294:13 300:1	145:15,15,18	285:2 291:10	<b>peripherally-a...</b>	307:2,4 330:1
303:17 305:1	145:18,19	291:20 292:3	135:2	352:7 371:13
335:12,16	146:4,4,16,16	292:10,14,19	<b>peripheral-to-...</b>	<b>pharmaceutical</b>
337:8 346:14	146:16,17	295:16 296:13	210:1	180:15 181:4
357:16	149:11 151:14	299:10	<b>peristaltic</b> 286:9	<b>pharmacies</b>
<b>PCAs</b> 30:1 378:4	151:15,16	<b>percentiles</b>	<b>permission</b>	87:19 90:4
<b>PCA-controlled</b>	154:1 157:6	47:15	368:11	178:4 180:20
335:4	158:2 159:20	<b>perfectly</b> 316:17	<b>permit</b> 64:14	181:16,17
<b>Pennsylvania</b>	159:22 160:6	<b>perform</b> 174:17	<b>permitted</b>	364:7
2:12,21 9:20	161:2,2 162:17	<b>performance</b>	127:12	<b>pharmacist</b>
<b>people</b> 109:19	162:19 181:17	160:17,19,22	<b>permitting</b>	20:16 177:6
127:20 191:11	189:7,8 202:12	162:2 172:15	24:20	363:15
195:9 200:22	202:13 208:21	266:4	<b>perseverate</b>	<b>pharmacists</b>
206:4 213:5,12	208:21 214:2	<b>performance-l...</b>	199:7	88:1 180:21
236:5 239:11	215:5 225:7,7	175:4 177:16	<b>persist</b> 154:18	181:18

<b>pharmacodyn...</b> 115:22	365:1	140:7 141:10	352:13 353:13	<b>pneumonias</b> 106:20
<b>pharmacodyn...</b> 115:19	<b>physicians</b> 81:14	142:1,16	353:14 359:7	<b>PO</b> 138:9
<b>pharmacoecono...</b> 287:3,10	181:11 261:21	143:14 144:5	360:7 361:4	<b>podium</b> 26:12
288:15	360:1	145:9,11,14	365:11 369:7,8	<b>POI</b> 21:6,10,12
<b>pharmacoepid...</b> 9:19	<b>physician's</b> 302:9	146:3,15 147:1	369:11,22	21:16 22:18
<b>pharmacokine...</b> 35:19 112:16	<b>physician-pati...</b> 177:12	149:17 150:19	370:3,4 384:17	23:13 24:5,17
<b>pharmacokine...</b> 115:19	<b>physiologic</b> 27:21 334:8	151:14 153:17	384:20 385:1,2	25:10,11,12
<b>pharmacokine...</b> 128:19	<b>pick</b> 250:20,21	154:3 157:19	<b>planned</b> 98:6	27:12,13,18,21
<b>pharmacologic</b> 35:18 95:8	251:1 285:6	158:3,7,22	368:19	30:10,17,21
<b>pharmacologi...</b> 85:13 209:6,10	<b>picked</b> 300:20	159:22 160:4,9	<b>plans</b> 172:21	31:4,9,11 32:5
<b>pharmacologist</b> 210:11	<b>picking</b> 251:2,4	160:13 161:2	179:15 183:2	32:8,12,13,21
<b>pharmacology</b> 35:16 76:9	338:21	161:12 162:19	322:16 360:19	33:19 34:6
166:7,7 167:9	<b>picture</b> 277:22	165:5 187:18	361:3	35:2 36:9
172:4,5 209:5	<b>piece</b> 289:4	200:15 206:6	<b>plaque</b> 319:7	37:12 40:21
223:21	321:12,13	215:15 225:3	<b>plasma</b> 38:20	41:11,20 42:8
<b>pharmacovigil...</b> 119:5	<b>pilot</b> 367:3	225:18 226:2	113:18 117:2	43:20 44:10
<b>pharmacy</b> 87:21	<b>Pirates</b> 359:9	229:1,17 234:5	<b>plausibility</b> 65:1	45:18,19 48:1
87:22 88:9	<b>Pittsburgh</b> 359:9	237:12 242:15	270:5	55:10 58:13
178:6	<b>PK</b> 38:19 113:17	242:17 248:16	<b>plausible</b> 91:10	59:17 60:20
<b>Phase</b> 22:20	115:1	263:1 265:5	221:16 222:7	62:1,5,11,20
35:7 37:12,14	<b>place</b> 7:7 87:14	267:8 284:12	269:13 279:20	63:8 76:2
38:13,14 48:1	87:17 127:7	321:10 323:18	<b>play</b> 99:17 236:8	77:12 78:4,7
78:16,17	132:15 182:10	323:21 324:2	359:11	78:10,12,14
137:10 153:6,6	197:16 223:3	345:10 349:5,6	<b>plays</b> 236:6	80:3,14 81:16
373:1,2,3,7,11	268:18 290:7	350:12 376:9	<b>please</b> 7:18,20	82:11,17,20
373:12 374:19	315:6 359:10	381:21	8:15 16:6 92:8	83:2,5 84:6
375:1,1 376:6	<b>placebo</b> 23:15	<b>placebo-contr...</b> 63:18 137:12	124:22 127:15	85:12 86:3
385:14	37:17 49:9,10	161:18	133:14 210:9	90:19 91:4,10
<b>phone</b> 7:21	50:13 51:7,10	<b>placebo-treated</b> 55:4 57:16	213:13 216:11	95:9 104:22
151:8 152:10	52:22 53:5,11	158:11	220:4 234:10	109:6,8 110:14
156:22 354:11	53:22 54:15	<b>placed</b> 126:14	236:17 241:17	131:3,12 132:6
<b>physical-chem...</b> 86:13 116:14	55:17 56:1,4	128:5	241:20 242:22	132:14 134:16
<b>physician</b> 33:2	57:2,7 58:17	<b>placement</b> 127:3	263:7 297:15	134:16,17
104:14 122:17	59:14 64:1	<b>places</b> 113:6	304:18 305:15	135:13,14,20
341:16 363:14	65:10 66:3	240:21 288:11	305:15 306:16	136:4,5,6
	67:2,17 68:22	<b>placing</b> 90:10	306:18 307:19	137:9 143:18
	69:12 72:15,17	128:1	328:8,18	144:6,13,14,18
	73:18 74:4	<b>plan</b> 20:7 24:9	330:15 351:7	145:1,8 146:18
	78:21 94:3	25:5,21 47:4	369:12 370:9	147:1,10,11,16
	96:16 102:13	84:22 85:3,6	370:12,14	147:19,22
	104:4 105:2	87:7 88:4 90:7	371:9	148:2,20,22
	106:1,22	91:16 109:17	<b>pleased</b> 201:14	149:3,5,6,14
	110:17 121:17	136:21 173:4	<b>plot</b> 155:10	151:3 152:4,8
	125:2 127:6	179:16 183:2	274:13	152:18 156:15
		279:13 280:4	<b>plus</b> 120:4	156:17 157:5,8
		322:21 323:6	154:12 162:13	162:4 165:16
			221:4	184:12 189:17
			<b>pneumonia</b> 31:7	

194:20 196:18 201:10 203:14 214:22 256:3 257:6,13 271:4 274:18,19 280:20 281:5 281:10 293:4 304:16 308:17 309:17 310:1 312:5 344:1 352:11 369:21 382:7 384:15 <b>point</b> 23:18 52:16 98:22 101:13 103:19 113:10 129:6 132:13 187:4 190:10 194:7 195:14 199:6 200:10,18 212:10,16 221:17 222:22 224:8,8 226:1 238:13,16 239:16 242:15 242:18,19 243:5,9 247:2 249:3 251:5 258:6 272:12 272:20 273:14 282:2 289:11 290:17 310:16 319:13 325:11 341:7 349:21 354:8 359:3 364:1 366:6 369:13 373:6 373:15 <b>pointed</b> 114:11 194:19 345:17 <b>pointing</b> 234:1 <b>points</b> 52:22 78:11 114:4 139:22 189:7 211:11 242:7 272:17 284:18 286:17 296:1 299:4 343:9	365:11 <b>Poland</b> 268:6 <b>policy</b> 246:18 <b>polled</b> 273:6 <b>polling</b> 245:22 <b>pooled</b> 156:7 204:20 255:7 255:11 257:17 258:8 325:6 364:18 <b>popular</b> 226:14 <b>population</b> 23:3 33:14 38:17,19 45:11 46:8,9 46:16 48:7 50:1,8 52:9 62:1,21 66:18 67:15 69:14 73:16 75:9 77:8,21 84:6 91:5 100:4,7 101:3 109:6,8 110:18 113:14 124:17 138:2 143:18 144:13 144:18 145:2,8 146:11,19 147:2 149:6,14 152:22 153:14 154:12 156:14 156:18 161:10 161:20 162:4 162:11,12 164:19,22 177:18 213:3,5 213:6,11 214:22 215:5,7 216:3 222:8 223:20 224:2 226:13,21 227:10 243:20 250:2 256:9,11 256:15 257:6 257:11 258:1,7 292:2 311:7 312:5 317:6 321:12 326:18 326:20 336:6	336:16 354:4 358:1 374:21 375:11 <b>populations</b> 17:19 22:21 32:7 51:19 78:4 161:7 257:3,8 361:6 376:7 <b>posed</b> 283:19 <b>positive</b> 54:3 57:3 84:17 169:19 170:4 172:11 271:21 281:5 372:13 <b>positively</b> 228:11 267:3 <b>possible</b> 85:3 115:9 128:5 148:17 181:14 230:9 232:21 257:9 354:2 <b>possibly</b> 161:13 <b>post</b> 43:1 48:9 198:12,13 274:5 299:20 <b>posted</b> 14:18 <b>postop</b> 27:7 83:22 98:10 125:6 193:21 219:19 271:16 275:8,10 276:9 276:16 278:7 285:9 335:5 <b>postoperative</b> 17:8 19:2 21:5 21:6 22:10,15 26:20,22 27:5 28:2 29:1,18 30:3 33:1,12 34:12,16,19 35:10 36:3 37:6 38:9 39:16,20,22 40:2,11 41:14 43:14 49:1 51:12 52:18 53:4,5 57:22	58:9,16 60:6 66:8 90:19 91:13 93:5 103:1,14 104:21 105:12 106:12 108:8 108:17 117:7 117:10 125:9 125:12 129:9 129:17 135:13 145:16 194:2 216:1 218:3 219:15 221:4 221:10,20 226:22 228:19 229:22 235:8 238:22 239:1 240:6 261:13 277:4 284:6 288:16 294:20 296:21 308:4 345:1 378:3 381:16 <b>postoperatively</b> 37:21 125:3 126:17,21 129:11 193:21 272:18 346:12 375:9 <b>Postsurgical</b> 44:8 55:3 57:15 254:16 255:1 <b>postulate</b> 319:9 321:20 <b>post-approval</b> 366:4,10,19 368:8 374:4 379:6 <b>post-drug</b> 201:18 <b>post-exposure</b> 152:14 <b>post-study</b> 70:1 71:13 <b>post-surgery</b> 46:12 138:9,11 189:18	<b>post-surveilla...</b> 368:7 <b>post-traumatic</b> 70:8 <b>potassium</b> 230:2 <b>potent</b> 36:11 37:18 311:21 <b>potential</b> 12:2,6 12:10,16 36:15 43:9 59:1 70:14,19 72:4 73:20 74:8 76:5 86:4 102:17 116:4,7 127:9 136:21 148:21 153:10 165:14 166:19 167:15 194:4 213:17 255:22 272:1 308:5,6 312:16 331:12 331:20 334:16 334:19,20,21 343:15 344:11 351:3 352:14 366:9 370:1 375:2,10,12,19 376:19 380:8 382:22 383:14 383:18 384:6 384:18 385:17 385:21 <b>potentially</b> 44:20 53:7 129:16 216:14 225:6 233:6 234:20 265:10 265:21 280:7 301:5 358:1 380:11 <b>potty</b> 330:6 <b>power</b> 280:22 <b>practical</b> 249:16 <b>practicalities</b> 250:13 <b>practice</b> 23:16 49:12 51:22 56:11 133:6,10
---	---	--	---	--

193:6 217:7 218:10 219:5 234:21 247:13 291:3 298:8 302:15,18 <b>practices</b> 39:18 143:5 176:16 <b>practicing</b> 81:13 <b>practitioner</b> 176:2 177:11 <b>practitioners</b> 175:21 176:4 178:3,5 <b>Precautions</b> 88:20 89:5 <b>precedence</b> 201:15 <b>precedent</b> 43:19 198:8 201:12 261:11 271:7 <b>preclinical</b> 76:4 76:6,11,21 156:10 165:21 258:19,21 259:5,8 <b>preclude</b> 172:1 <b>predefined</b> 102:15 <b>predicate</b> 365:14 <b>predicated</b> 272:15 357:9 <b>predict</b> 27:10 34:15 244:8 278:12 <b>predicted</b> 156:9 <b>prediction</b> 381:4 <b>predictive</b> 111:11 <b>predictor</b> 74:7 94:19 <b>predictors</b> 356:21 <b>predominantly</b> 73:1 <b>predominate</b> 156:20 <b>prefer</b> 369:1	<b>preferred</b> 43:7 <b>pregnancies</b> 360:21 <b>pregnancy</b> 178:15 <b>preliminary</b> 19:11 <b>premise</b> 106:9 <b>preop</b> 356:3 <b>preoperative</b> 93:22 103:8 111:17 129:10 129:17 272:4 275:21 365:20 <b>preoperatively</b> 37:17 272:6 274:11 275:19 <b>preparation</b> 92:17 <b>prepared</b> 193:16 <b>preponderance</b> 282:10 <b>prerequisite</b> 379:14 <b>prerogative</b> 271:12 <b>prescribe</b> 221:3 357:22 <b>prescriber</b> 177:10 <b>prescribing</b> 176:16 177:21 <b>prescription</b> 176:18,21,22 <b>Prescriptions</b> 178:2 <b>presence</b> 28:4 75:11 269:16 <b>present</b> 7:20 19:10 25:13,14 44:1 60:20 61:8 134:9 144:7 166:1 172:22 236:12 250:10 268:22 283:4 311:22 <b>presentation</b> 16:13 20:13	25:6 35:15 45:19 46:5 60:15 92:3,15 134:1,11,14,21 136:16 156:11 180:4 184:16 189:6 193:4 198:19 231:5 247:20 297:9 326:11 358:5 358:10 <b>presentations</b> 16:8 <b>presented</b> 24:15 39:13 47:2 49:19 85:16 133:19 197:22 199:11 205:7 211:21 212:5 239:19 240:1 295:8 <b>presenter</b> 16:5 20:15 <b>presenters</b> 183:19 <b>presenting</b> 63:15 206:13 <b>presents</b> 154:20 155:2 <b>president</b> 20:17 20:20 26:17 287:7 <b>prespecified</b> 102:15 105:18 <b>press</b> 7:16 8:15 92:9 330:16,20 <b>pressure</b> 259:3 <b>presumably</b> 203:17 <b>pretty</b> 93:21 103:16 114:3 132:8 210:2 226:2 296:2,5 298:16 <b>prevent</b> 85:8 181:2 183:9,10 221:4 275:7 276:2 333:10	357:18 360:20 <b>preventable</b> 31:22 178:22 360:9 <b>prevented</b> 173:20 <b>preventing</b> 27:15 33:11 <b>prevention</b> 34:11 361:13 385:3 <b>previous</b> 106:11 202:7 272:15 296:15 374:5 <b>previously</b> 31:9 50:21 109:14 112:9 227:22 296:11 <b>pre-existing</b> 71:19 109:18 228:15 <b>pre-malignant</b> 70:10 <b>pre-specified</b> 42:20 46:17 47:3 64:13 68:10 139:19 <b>primarily</b> 48:14 51:10 67:22 77:7 99:10 110:19 132:7 250:3 361:12 <b>primary</b> 8:9 13:4,12 16:21 17:13,22 18:14 29:4 30:20 31:3 37:9 40:6 41:2,22 42:19 44:15 45:3,7 46:17 48:8 49:4 50:3,10 58:7 70:13 85:7 104:15 112:6,20 123:21 124:1 135:11 138:21 139:3,19 141:4 148:9 185:1	192:21 198:14 217:4 307:12 328:4 331:15 351:5 382:15 <b>principal</b> 66:21 <b>principally</b> 75:22 <b>prior</b> 10:16 20:5 40:20 57:15 59:20 63:14 64:12 65:19 66:13 71:20 89:4 138:7 140:22 224:9 <b>priori</b> 315:9 <b>private</b> 133:6 <b>privilege</b> 35:6 <b>proactively</b> 34:20 <b>probability</b> 53:3 266:9 <b>probably</b> 18:4 94:16 108:15 119:3 133:9 186:13,15 206:6,8,16 207:2 208:13 220:5 227:2,2 238:10 245:1 263:11 280:21 288:22 295:14 315:5 316:20 337:19,22 341:22 342:3 342:18 360:17 363:17 365:21 373:19 375:5 375:15 380:14 <b>problem</b> 27:1 126:20 148:17 149:1 191:5 198:17 260:3 288:13 290:20 300:14 309:6 312:5,19 317:4 317:5 375:17 376:6 378:12 378:14
--	---	--	---	---



112:15	287:20 343:5	263:4,10,18	92:6,7,18	239:16 304:4
<b>pull</b> 222:4	344:22 345:12	264:5 267:17	93:12 94:14	305:15 306:17
<b>pulled</b> 125:17	<b>quantified</b> 332:2	267:18,21	99:6 100:1	318:12 351:7
<b>pulmonary</b>	<b>quantify</b> 94:22	268:14 269:16	101:16 115:18	369:12 370:9
30:14 32:3	96:22 332:6	271:12 272:11	118:5 121:4	370:12 371:9
347:4	<b>quantile</b> 250:20	272:14,16	130:15,18,20	<b>raised</b> 82:22
<b>pump</b> 193:21	250:21 251:3	276:7 277:10	144:2 183:18	211:16 220:22
276:14	252:7,10	277:11,13	194:15 196:2,3	272:21 293:16
<b>pumps</b> 29:20	<b>quantiles</b> 251:13	280:10,12	206:11 211:13	308:3 315:20
<b>purchases</b>	253:5	281:14 284:1,2	212:13,21	316:13 322:8
182:17	<b>quartiles</b> 97:4	284:4,22 285:4	213:2 258:19	352:19
<b>pure</b> 376:6	<b>question</b> 82:22	285:16 292:6	262:18 277:10	<b>randomization</b>
<b>purely</b> 196:9	93:3,4,14 94:6	292:22 293:1,2	277:12,15	71:20 234:18
270:1	98:4,12 100:3	293:3,16 296:7	283:18,20	<b>randomize</b>
<b>Purkinje</b> 167:13	101:14 102:7	297:3 298:19	308:16 330:18	376:9
207:13	106:7 107:2,3	298:21 300:3	339:13 343:11	<b>randomized</b>
<b>purpose</b> 176:13	107:10 108:1,2	302:15 304:2	352:19 368:12	63:18,21 72:14
177:17 233:14	113:11 120:22	304:14 305:6,8	381:8,12	137:11 232:8
<b>purposes</b> 12:20	121:4,20 122:4	307:5,6,7,17	<b>question's</b> 108:6	234:7 235:1
340:18 380:21	124:20 126:8	314:22 315:6	<b>quick</b> 267:16	333:22 373:7
<b>pursue</b> 377:1	126:13 127:2	315:20,20	286:5 327:3	373:14 375:14
<b>push</b> 245:6	127:14 129:20	316:13 317:1,2	<b>quickly</b> 218:5	378:7
<b>put</b> 20:3 87:13	129:22 130:13	321:8 322:13	227:12 267:20	<b>randomizing</b>
125:8 137:1	131:15 133:12	326:7 327:20	367:15	378:3
191:1 197:16	180:1 187:21	330:4,4,12,22	<b>quintiles</b> 96:22	<b>randomly</b>
202:22 204:22	188:3 189:10	331:2,9,10	<b>quite</b> 6:17 61:22	250:22 251:2
226:9 248:11	191:20 192:1	335:14,19	70:7 103:6	<b>range</b> 34:9 52:4
264:6 305:22	193:13,18	341:6,15	127:19 191:8	57:7,10 70:11
306:7 307:16	194:14 195:15	343:22 344:20	200:2 204:10	70:16 95:22
315:6 318:18	195:18 196:6	350:20,22	228:1 229:21	213:22 218:12
328:19 349:12	196:22 197:19	352:10,11	238:10 241:3	254:11 320:20
354:2 356:14	207:7,7,9,20	354:14 355:6,7	246:17 257:7	<b>ranged</b> 34:4
358:13,22	208:1 210:6,12	366:10 368:13	258:14 261:8	50:14 135:6
366:22 383:13	213:17 214:8	368:14 369:16	263:16 304:12	255:9
<b>putting</b> 112:15	215:1 216:11	369:19 371:16	337:7 358:19	<b>ranging</b> 55:3
288:7 350:2	217:15,18	371:17 374:5	359:2	56:2,5 57:20
359:22	218:7,22 219:9	375:3 378:5,8		<b>rant</b> 317:18
<b>pyrexia</b> 79:16	220:20,22	378:15,20	<b>R</b>	<b>Rapids</b> 26:18
<b>P&amp;T</b> 287:11	226:9,12,19	381:14,15	<b>R</b> 3:14 6:1 211:1	213:20
<b>p.m</b> 56:17	227:22 228:18	382:5,9 383:16	<b>rabbits</b> 166:15	<b>rare</b> 80:8 257:1
210:18,21	229:3,19 233:6	384:14 385:5	166:18 167:5	257:12
211:2 386:3	233:21 234:1	<b>questionable</b>	172:16	<b>rarely</b> 163:1
	235:4,4,5	317:21	<b>race</b> 54:21	<b>rat</b> 170:10
<b>Q</b>	236:10 241:17	<b>questioning</b>	<b>radiographic</b>	172:12
<b>QD</b> 147:18	245:19 247:17	222:11	208:7	<b>rate</b> 32:20 50:6
<b>QT</b> 76:15 168:3	249:12 253:20	<b>questions</b> 16:6	<b>radiography</b>	67:4 88:12
<b>qualify</b> 374:15	254:9 256:6	18:19 26:2	64:5 75:1	103:5 104:3
<b>quality</b> 83:3	257:15 259:8	70:15 83:13	<b>raise</b> 92:8	105:10,17,21

162:18,19	350:20 369:16	199:10 203:2,3	248:3 283:7	208:14 209:2
221:9 226:22	<b>readily</b> 87:4	203:4,6 215:18	316:3 322:10	210:7,13
227:3 231:10	<b>reading</b> 107:13	217:3 219:15	343:19 380:12	235:22 236:1
256:15 324:2	339:11 360:7	220:21 221:10	<b>reasonable</b>	<b>recess</b> 133:21
338:3 362:11	<b>readmission</b>	222:15 223:6	97:15 204:8	210:22 330:13
362:12,13	44:12 104:3,16	233:12 235:18	260:15 348:19	<b>recognize</b> 77:19
<b>rates</b> 69:21 80:2	104:22 105:4,9	236:21 237:7	<b>reasonably</b>	85:10 185:16
80:21 81:2	105:21,21	238:11,20	163:10	198:11
106:3 107:6	254:19	239:12 240:13	<b>reasons</b> 14:16	<b>recognized</b> 7:1
159:16 161:21	<b>readmissions</b>	243:18 245:2	52:5 73:21	21:9 224:3
163:10 165:8	90:22 104:11	246:10 249:1	127:8 155:18	304:6
171:16 175:10	106:8	251:3 260:1	232:21 285:15	<b>recognizing</b> 69:3
<b>rate-limiting</b>	<b>readmitted</b>	261:1,6,16,21	365:18 376:3	198:3
42:7	106:16 216:18	262:1,8,9,12	<b>reassurance</b>	<b>recommend</b>
<b>ratio</b> 24:20	240:19 247:9	262:13 264:21	277:16 280:1	20:5 129:16
46:21 50:11	<b>ready</b> 18:6,8	269:12 271:1	<b>reassuring</b>	375:13
64:1 72:16	43:4 55:15	276:8,21	198:20	<b>recommendati...</b>
124:7 210:1	114:16 139:8	277:15 278:15	<b>rebuttal</b> 212:17	93:18
265:3 266:12	139:10,11	286:16 289:11	<b>rebuttals</b> 349:18	<b>recommended</b>
267:9 309:7	141:17,18,18	289:16 290:17	<b>recall</b> 120:9	33:20 171:12
346:8 378:9	141:22 240:10	291:10 294:10	254:13 326:10	<b>reconstruction</b>
385:16	290:10 293:8	295:19 296:13	349:4	221:16
<b>rationale</b> 36:2	298:22 299:12	308:16 309:15	<b>recalls</b> 212:21	<b>record</b> 7:1 15:12
128:4	300:12,19,22	310:10 311:3	<b>receive</b> 40:9	15:22 133:20
<b>rationalize</b>	302:3,12,17	312:7,18 315:8	86:8 93:10	234:11 284:4
292:1	340:16 382:3	316:6 318:17	96:12 108:21	304:2 325:14
<b>ratios</b> 53:19 54:2	<b>real</b> 157:9 162:8	318:21 332:22	217:17	326:4,12
54:9,21 55:15	190:21 257:2	334:16 335:18	<b>received</b> 14:1,6	342:12
56:22 58:6	309:6 313:1	336:1,5 346:11	24:4 37:16	<b>recorded</b> 215:7
114:14 140:10	321:4 325:5	348:16 353:19	40:18 63:11	304:7 306:7
141:12 142:2	333:12 343:17	354:5,12	78:20 79:8	329:9
222:21 225:10	343:19,21	356:18 358:12	85:1 89:3 96:7	<b>recording</b>
309:20	349:10 384:8	358:14,22	127:11 144:16	122:12
<b>rats</b> 166:15,18	<b>realistic</b> 362:4,8	359:11,21	157:19 160:9	<b>records</b> 83:18
167:2,5,18	<b>realistically</b>	362:20 363:9	160:13	273:17,18,19
168:15 169:11	337:19	385:1	<b>receiving</b> 39:1	<b>recover</b> 30:6
169:12 172:15	<b>reality</b> 321:5	<b>reanalyzed</b>	55:2,14 86:6	189:20
172:16 208:7	340:14 364:9	149:1	95:19 174:19	<b>recovering</b>
209:7	<b>realize</b> 19:12	<b>reason</b> 30:19	242:16 262:22	237:1
<b>RB</b> 379:2	358:3 364:1	50:3 51:9	275:16 385:18	<b>recovery</b> 8:6,7
<b>reach</b> 87:21	366:15	62:16 95:17	<b>receptor</b> 21:19	13:10 16:19
316:20 318:11	<b>realizing</b> 105:16	96:21 100:6	36:6,21 37:8	18:9 22:3 28:1
<b>reached</b> 88:13	105:17	114:8,12	38:22 94:18	30:8,22 31:2
140:17	<b>really</b> 98:21	130:11 151:21	207:10 215:20	41:1,17,19
<b>read</b> 6:9,11	101:6 102:4,10	161:16 186:16	236:5,7 274:16	42:2,3,12 43:6
10:17 211:18	105:18 109:20	187:16 217:4	<b>receptors</b> 29:10	44:1,14 49:4,6
304:2 311:15	111:10 118:10	222:16 234:4	36:12,14,19	50:14 52:11
327:20 348:13	152:16 188:13	239:3 245:3	130:9 208:2,4	53:3,11 54:11

54:13 55:3,9 55:22 59:12,19 90:15 96:11 98:15 100:12 101:18 108:14 123:2 126:11 135:10 138:15 138:16,18 139:12,17 143:2,8,20 144:3 146:9 193:2 236:17 237:21 239:20 241:20 243:7 243:19 244:4,9 244:10 246:4 284:7 381:18	<b>reflecting</b> 67:4 <b>reflects</b> 209:16 <b>refocus</b> 352:18 <b>refrain</b> 7:12 133:18 <b>regard</b> 18:16 93:18 110:5 120:17 132:18 143:6 219:9 234:17 268:13 271:4 281:13 307:12,22 328:5 330:21 382:16 <b>regarded</b> 338:3 <b>regarding</b> 17:13 19:18,19 28:10 82:5 83:1 115:20 197:20 211:20 214:14 217:15 310:6 <b>regardless</b> 54:20 216:1,17 237:4 254:6 258:12 <b>regards</b> 325:8 <b>regimen</b> 130:12 147:16 <b>regimes</b> 220:7 <b>region</b> 231:9 <b>regional</b> 49:12 234:21 <b>register</b> 182:9 374:11 <b>registered</b> 20:16 178:18 211:8 <b>registration</b> 15:3 <b>registries</b> 324:16 360:20 362:19 363:6 <b>registry</b> 203:18 322:18 362:9 <b>Reglan</b> 228:20 <b>regrets</b> 15:6 <b>regular</b> 11:8 12:9 <b>regulate</b> 361:17 <b>regulations</b>	11:10 <b>regulatory</b> 20:17,20 134:16 136:1 198:9 <b>rehabilitation</b> 181:8 <b>reimbursement</b> 287:19 <b>reinforce</b> 343:12 <b>reinforcing</b> 89:19 342:8 <b>reinserted</b> 125:14 <b>reinsertion</b> 125:7 346:17 349:8 <b>reinsertions</b> 126:2 <b>reintroduce</b> 211:14 <b>reiterate</b> 290:6 <b>relate</b> 116:5 <b>related</b> 12:13 28:16 49:11 77:7 101:15 102:1 103:7 104:2 106:12 193:22 201:7 216:10 226:12 229:19 258:19 263:5 265:10 <b>relates</b> 149:3 224:7 <b>relating</b> 30:22 195:21 <b>relationship</b> 76:18 95:7,16 97:4,6 128:19 163:22 269:8 270:5 <b>relationships</b> 16:2 65:2 76:18 <b>relative</b> 43:17 64:2 65:15 67:6 68:4 70:2 71:9 72:1	75:19 81:4 116:2 126:4 144:5 158:8 179:3 200:19 284:11 326:21 360:12 381:21 <b>relatively</b> 19:4 130:3 199:8,16 226:4 232:9 256:13 312:4 341:11 345:4 363:20 375:20 384:4 <b>release</b> 235:21 <b>released</b> 28:18 132:2 <b>releasing</b> 280:6 <b>relevance</b> 171:20 302:16 302:17,17 <b>relevant</b> 18:4 42:14 66:8 91:10 122:22 153:6 188:9 298:8 301:16 301:20 <b>reliable</b> 34:14 <b>relied</b> 261:17 <b>relies</b> 179:20 <b>relieve</b> 58:8 <b>relying</b> 293:10 295:6 <b>remain</b> 52:17 155:16 262:19 <b>remainder</b> 46:5 <b>remained</b> 38:1 38:21 <b>remains</b> 52:21 77:19 376:4 <b>remark</b> 362:1 <b>marking</b> 226:1 <b>remarks</b> 61:17 <b>remember</b> 191:17 240:2 242:2 244:13 246:12 254:12 281:17 304:10	325:21 <b>remind</b> 7:19 15:15 <b>reminder</b> 6:21 175:2 176:12 176:14 177:9 <b>removal</b> 33:4 39:19 <b>remove</b> 87:18 126:13 <b>removed</b> 125:11 <b>renal</b> 166:11 <b>rep</b> 9:16 <b>repair</b> 221:22 <b>repeat</b> 326:6 <b>repeated</b> 383:3 <b>repeating</b> 56:10 <b>rephrase</b> 253:22 <b>replicated</b> 76:1 78:2 108:19 110:8 <b>report</b> 271:15 273:11,22 <b>reported</b> 13:14 43:13 70:1 71:13 74:15 79:13 157:6 158:5,21 159:7 163:20 164:9 201:1 <b>reporting</b> 122:11,16 123:15 183:3 311:9 323:2 372:10 <b>reports</b> 44:10 65:3 69:5 70:5 73:7 88:6 179:17 254:17 254:17 <b>represent</b> 52:10 96:17 105:7 <b>representation</b> 248:14 <b>representative</b> 2:17 11:6 15:7 15:12 <b>representatives</b>
---	---	---	---	--

7:15 15:9	238:13 367:20	90:18	372:13	296:4,9 299:15
<b>represented</b>	<b>resection</b> 8:8	<b>resources</b> 31:13	<b>responses</b> 23:3	304:15 308:19
42:2,15 56:9	13:11 16:20	363:4	129:3	382:7
145:5 234:14	21:5,16 22:2	<b>respect</b> 46:2	<b>responsibility</b>	<b>resume</b> 20:12
<b>representing</b>	23:5,7 24:2,18	48:14 49:3	358:18	<b>Resumption</b>
53:6	27:1,9 29:19	67:17 69:20	<b>rest</b> 130:15	42:6
<b>represents</b> 91:20	30:21 31:11	70:21 71:4	<b>rested</b> 27:19	<b>retail</b> 87:19,21
291:16	34:20 35:11	76:5 77:13	<b>restrict</b> 229:6	91:18
<b>reproducibly</b>	38:17 39:8	95:11 97:16	<b>restricted</b> 48:17	<b>retain</b> 182:16
239:2	40:6 42:13	98:20 100:4	175:3 177:15	183:6
<b>reproductive</b>	44:16 45:3,5,7	102:2 127:3	177:16 356:12	<b>retention</b> 74:10
167:3 172:12	45:10 46:14,16	129:2 219:6	<b>restriction</b> 354:2	<b>retrospective</b>
172:14	48:7 50:1,8,21	225:18 243:18	<b>restrictions</b>	205:17
<b>request</b> 14:21	50:22 51:17	259:13 337:8	177:21	<b>retrospectively</b>
61:1	52:8,11 53:18	346:21 348:17	<b>result</b> 68:12 79:3	44:5 312:22
<b>requested</b> 24:10	55:11 58:21	<b>respective</b> 253:5	91:19 132:15	<b>returned</b> 38:8
136:19	59:10 60:12	<b>respectively</b>	174:11 201:5	<b>reveal</b> 32:18
<b>requesting</b> 85:2	78:19 82:7,13	51:3 161:3	203:2,6,9	<b>revealed</b> 34:4
213:21	83:18 84:19	<b>respiratory</b>	242:4	<b>reversal</b> 84:13
<b>require</b> 33:2	85:19 89:17	103:2	<b>resulted</b> 44:12	<b>reverse</b> 129:4
55:7 64:4	90:2 97:17	<b>respond</b> 122:7	59:10 88:12	173:19
77:20 87:14	100:6 101:8	127:14 188:17	<b>resulting</b> 46:20	<b>review</b> 15:2
98:7 119:15	110:19 115:15	189:2 245:20	67:5 68:19	23:12 24:3
127:22 177:2	135:11 137:14	256:6 277:3	80:8 90:15	25:5 35:13
179:5 182:7	138:2,5 145:4	298:11,13	<b>results</b> 22:2	64:19 65:4,5
188:4 305:1	146:11 162:8	368:3	30:18 35:3,7	68:15 70:5
315:4 324:17	196:1 205:11	<b>responder</b> 43:20	35:14 39:4,12	83:18 119:11
327:6 360:14	206:17 215:6	44:2,6,17	44:1 45:1,19	136:12 137:7
364:7 375:8	221:6 226:15	47:19 189:19	46:3 47:7 48:3	140:20 141:1
<b>required</b> 36:9	248:4,5 255:8	254:10,13,14	48:6,11 49:20	148:7,20 196:7
40:3,9 41:20	256:12 261:14	255:5	50:17 53:15	196:13 233:3
62:4 63:2 98:6	278:17 288:1	<b>responders</b>	54:8 55:18	<b>reviewed</b> 47:22
125:11 140:21	307:12 328:4	59:19 188:21	56:3 58:4	76:4 164:4
178:15,16	335:4,10,11	188:22 255:11	60:10 61:14	<b>reviewer</b> 148:9
195:12 272:4,8	339:17 356:12	255:14	65:14 68:1	<b>reviewing</b>
273:11 293:20	365:2 382:15	<b>responds</b> 285:4	72:7 82:1	159:14
374:3	<b>resections</b> 17:22	<b>response</b> 23:4,10	84:15 114:1	<b>revisit</b> 340:3
<b>requirements</b>	22:22 27:2	27:18 28:13,19	115:14 134:17	<b>re-consented</b>
88:5 123:10	51:21 126:12	35:20 65:2	134:17 139:16	196:5
<b>requires</b> 179:1	221:11 298:2	76:18 95:13	139:17 140:19	<b>re-consenting</b>
<b>requiring</b> 52:8	331:14 341:2	97:6 112:5	141:16 143:9	196:22
72:8,12 176:22	351:5 383:20	113:3 114:21	144:6 145:20	<b>re-consents</b>
<b>reread</b> 369:18	<b>resective</b> 375:8	129:2 136:12	161:12 166:1	197:10
<b>research</b> 1:2	<b>Reserve</b> 127:18	137:7 186:19	169:18 191:3,3	<b>re-operated</b>
3:10,20,22 4:4	133:3 238:9	188:5 249:8	194:17 202:20	314:1
4:6,8,10,12,14	<b>resolution</b> 22:2	258:16 272:13	202:22 224:5	<b>re-rebuttal</b>
9:19 26:17	38:7 41:20	338:3 341:12	260:22 285:12	212:19
81:12 117:9	42:8 55:10	361:12 367:22	293:4 294:14	<b>re-rebuttals</b>

<b>rib</b> 162:6	149:5 154:5	384:22	378:9	<b>Royce</b> 303:18
<b>ribs</b> 163:3	155:7,13,20	<b>RiskMAP</b> 173:3	<b>Rita</b> 7:17	<b>rule</b> 124:5
<b>Richardson</b> 3:12	156:1,13 158:9	173:4,7,8,9,21	<b>ROBERT</b> 3:6	234:20
9:11,11 121:2	164:1,7 172:21	174:3,10,10,15	<b>robust</b> 24:1,14	<b>running</b> 347:2
121:3 123:3,6	173:3,14 174:2	174:20 175:9	39:5 54:17	<b>rush</b> 126:13
123:9,13 125:6	179:10,19	175:12,17,18	56:5 95:13	<b>Ruyi</b> 4:5 10:8
125:21 195:17	187:10 194:18	176:7 178:19	97:18 114:20	134:2,7
195:18 196:21	195:4,22 197:1	178:21 179:6,8	237:14 258:15	
297:19,20,20	201:6,13,17	179:9,11,17,18	302:22 325:21	<b>S</b>
306:19,19	211:17 212:6	179:20 180:13	366:9	<b>S</b> 2:7 6:1 211:1,1
329:2,2 336:20	214:12,21	180:14 182:2	<b>Rochester</b> 9:12	211:1
336:21 352:4,4	222:1 226:4	182:11,22	<b>role</b> 29:7 229:21	<b>SAEs</b> 80:7
355:13,14	234:22 248:22	183:3,12,14	236:6,8 318:16	146:20
371:1,1	249:3 256:13	338:7 355:16	<b>roll</b> 8:10	<b>safe</b> 25:3 91:12
<b>right</b> 52:2 93:12	257:8,9,9	358:20 360:8	<b>rolled</b> 206:5	177:12 178:14
96:6 115:8	263:3,3 265:3	360:11,14	<b>rollover</b> 206:2	178:22 182:7
122:3 123:6,14	265:19 267:3	361:9,12	<b>Rolls</b> 303:18	183:13 278:21
124:12 125:21	269:9,11,15	364:21 365:7	<b>Ron</b> 9:11	280:7 360:9
133:1 184:10	270:19 271:3,9	366:17 367:19	<b>RONALD</b> 3:12	381:1
189:4,5 191:9	275:17 279:12	368:13,15	<b>room</b> 14:22	<b>safely</b> 90:7
239:15 245:4	282:3,21 313:9	<b>RiskMAPs</b>	126:11 210:19	<b>safety</b> 13:6
248:5 249:7	313:13 314:7	172:21 173:1,9	244:21 286:7	16:16 17:6
282:9,14	314:17 315:7	173:11,13	290:16	19:1,4,17,18
293:22 298:16	315:10,18	174:6 175:6,10	<b>roped</b> 210:19	19:20 21:3
301:11 323:3	317:7 319:10	175:13	<b>ROSENTHAL</b>	22:17 23:11
344:3 353:11	322:4 326:9,21	<b>risks</b> 70:2 81:4	2:14	24:5,11,14
356:6 362:19	328:17 331:4	152:20 155:11	<b>Rosing</b> 3:14 8:14	25:14,17 39:9
367:4	333:22 334:2	173:7 175:20	8:17,17 107:9	45:14,19 60:15
<b>rise</b> 107:14	334:18,19,20	177:20 178:22	187:6,7 296:6	60:20 61:15
<b>risk</b> 10:4 20:7	335:15 338:20	179:4,5,21	306:14,14	64:3 71:17
24:9 25:4,21	339:22 340:22	180:3 196:3	315:12,13	77:22 78:7,10
31:22 41:11	341:21 347:7,9	200:19 280:20	329:17,17	78:12,14 83:5
44:21 51:20	348:16 349:13	314:22 317:21	348:5,8 351:11	84:6,11,15
53:8 59:17	350:2,3,16	331:12 344:15	351:12,12	91:4 115:3
64:17 65:15	351:7 352:13	345:6,12 346:4	352:17,18	120:11 134:10
66:7 67:6 68:4	353:13,22	351:3 352:14	353:7 371:7,7	134:17,19
69:5 70:20	354:15,20	356:5 359:5	<b>ROTH</b> 2:11	136:20 144:12
71:9 72:1	355:2 357:1,5	360:5,8,13,14	<b>roughly</b> 143:21	144:14 146:18
75:10,13,15,19	357:8 358:1,8	360:21 361:5	144:1 189:12	148:6,14,17,18
77:13,16 84:11	360:6,18 361:2	372:3 375:10	189:14,16,22	148:21 149:4
84:21 85:2,3,6	361:3 362:16	382:19,20	224:21	152:10,22
85:19 87:7	362:17 365:11	383:9,18 384:8	<b>rounding</b> 288:22	153:10 161:14
88:16 90:7	369:6,8,10,22	384:18 385:16	<b>route</b> 167:20	165:12,14,17
91:15 93:7,8	370:1 375:16	<b>risk-benefit</b> 20:3	<b>routine</b> 372:10	166:7 167:9
106:11 109:13	378:13,16,21	173:18 334:12	<b>routinely</b> 33:10	172:4,5 173:5
109:16,19	379:12,13,20	348:7 361:8	83:19 246:16	174:4 175:20
110:17 111:20	383:5 384:6,12	385:15	273:16	180:11 186:20
134:22 136:20	384:13,16,20	<b>risk-to-benefit</b>	<b>royalties</b> 13:4	186:22 196:8

196:17 197:5 197:20 204:14 204:20 235:4 235:18 256:2,4 256:19 257:1,4 277:17 281:19 287:1 308:11 318:12 323:7 327:4,8 353:14 366:21 367:1,7 371:18 375:14 376:10 377:4 380:11 385:7 385:11 <b>safety-related</b> 173:22 174:7 <b>safe-use</b> 182:10 182:12 <b>sake</b> 342:3 <b>sales</b> 90:3 180:17 381:3 <b>sample</b> 195:2 <b>samples</b> 87:13 274:19 <b>San</b> 10:2 92:13 <b>sandwich</b> 289:4 <b>sarcoma</b> 170:2 171:5 <b>satisfaction</b> 30:1 365:15 <b>satisfy</b> 123:10 380:15 <b>save</b> 187:22 239:10 255:21 288:1,16 297:1 301:3 333:20 <b>saving</b> 288:7 301:5 312:11 <b>savings</b> 303:8,9 303:9 312:10 <b>saw</b> 23:2 67:21 73:16 82:16 97:13 101:8 108:12 110:7 111:3,7 128:17 180:4 185:11 218:16 239:22 264:10 265:10	265:15 267:8 270:21 279:16 292:4 324:13 343:9 360:2 <b>saying</b> 107:18 124:13 232:15 266:14 280:7 280:18 327:6 343:12 377:8 378:1,19 <b>says</b> 327:7 376:7 <b>scattered</b> 324:22 <b>scenario</b> 186:20 <b>schedule</b> 211:5 <b>scheduled</b> 40:5 40:15 228:20 <b>Schmith</b> 5:12 274:8,9,9 <b>School</b> 2:10,13 2:21 4:18 6:7 26:5 <b>science</b> 302:16 376:19 380:10 <b>Sciences</b> 2:5 <b>score</b> 40:4 266:3 266:4,7 <b>scores</b> 59:5 160:19,22 262:21 266:3 <b>scouring</b> 273:16 <b>scram</b> 330:20 <b>screen</b> 93:10 <b>screened</b> 12:16 93:6 <b>screening</b> 111:17 259:6 <b>se</b> 251:20 <b>Sean</b> 2:21 9:18 220:22 280:21 360:3 <b>seat</b> 307:16 <b>second</b> 69:19 81:6 88:16 93:4,14 100:3 121:13 124:20 126:15 127:13 129:19 131:15 136:12,18	137:6 141:1 170:15 185:2 192:1 193:12 196:13,14 233:3 239:14 246:19 268:13 282:2 317:3 364:16 368:14 374:21 <b>secondary</b> 18:5 42:21 58:7 70:13 82:14 112:21 139:9 139:21 141:19 142:6 162:7 163:16 165:5 185:14 <b>secondly</b> 121:13 270:7 300:8 354:1 <b>secret</b> 304:12 <b>secretion</b> 29:14 <b>section</b> 88:21 89:5 <b>security</b> 210:20 <b>see</b> 18:18 32:6 67:6 71:7,13 71:20 75:21 79:14 81:7 82:9 94:1,22 95:6,9 96:3,5 96:10,13,15 97:3 102:17 103:10 104:17 104:21 105:9 105:15 106:19 107:4,8 108:15 110:6,12 111:11 113:18 114:14,19 117:19 119:17 121:12 124:2 126:3 140:3,15 141:3,6,20 142:8,19 149:15 151:5 170:18 171:5 182:14 185:9	186:20 187:17 188:1,22 190:1 193:4 197:7 204:18 205:11 215:4 217:7,9 218:19 220:17 223:6,14 224:17,21 225:8,15,20 228:8 229:14 233:5,10,17 234:13 237:4 237:13,17 239:18 241:4 241:11,16,17 242:2,6,16 243:1 250:19 255:6,13 257:20 258:3 258:11,13,15 263:3,20,22 264:20 265:4 266:11,12 267:2 270:4,20 273:8 274:21 275:3 278:5,6 279:3,13 280:19,20,22 282:7,11 295:7 305:10 308:10 308:19 318:8,9 320:22 321:6 322:16 323:8 325:5 326:19 330:20 333:17 335:2 337:11 337:14,20 338:1,4 343:19 345:7,18,19 346:2,3 347:9 348:16 350:3 353:21 354:21 361:13 362:10 368:2 374:12 375:9 381:7 <b>seeing</b> 99:14 212:4 220:14 231:13 242:1	252:20 264:9 266:16 270:22 271:1 341:17 347:6 366:16 <b>seek</b> 219:21 <b>seeking</b> 18:11 22:15 120:10 276:19 <b>seen</b> 56:3 64:12 65:15 70:2 78:16,22 82:15 83:13,20 84:11 84:16 91:8 101:21 129:1 151:13 154:22 156:7 161:14 161:21 163:1,4 165:8 194:9,20 226:5 240:20 259:1 267:2 270:7 273:4 282:16,18 345:4 350:9 360:19 373:16 379:13 <b>segmental</b> 35:10 <b>selected</b> 73:1 139:22 <b>selection</b> 182:5 <b>selective</b> 21:18 36:4 215:19 <b>selectivity</b> 116:4 <b>sell</b> 180:16 <b>Senagore</b> 5:13 25:10 26:12,13 26:15 41:6 90:17 103:22 108:2,6 213:16 213:19,19 217:6 218:9 219:4,8 220:1 220:5,20 221:7 222:2 226:20 227:8,17 236:14 237:9 244:8 273:2 275:13 294:1 <b>send</b> 245:6 289:8
--	---	---	---	---

300:3,7	236:19 302:22	240:14	371:20 372:4	133:8 142:10
<b>senior</b> 35:5	364:18 379:20	<b>shifts</b> 56:13	372:16 376:22	147:15 150:20
<b>sense</b> 195:11	<b>sets</b> 32:6	<b>shipment</b> 88:8	377:2 383:19	170:14,16
260:1 299:19	<b>setting</b> 22:11,14	<b>shipments</b> 88:15	385:8	231:3 295:11
299:22 310:10	24:19 61:10	<b>shipped</b> 88:8	<b>Shoshan</b> 210:10	346:16
316:11 317:19	80:6 88:3	182:20	<b>show</b> 21:14	<b>side</b> 86:10 109:3
343:5,10 345:8	101:7 174:2	<b>short</b> 101:5	23:14 70:10	109:20 192:6,6
353:18	294:20 305:2	130:3 156:21	96:6 100:19,21	281:15 331:17
<b>sensitizes</b> 62:8	335:12,16	205:5 279:6,15	102:19 104:10	332:15 334:17
<b>sentence</b> 369:20	357:11 363:20	280:22 281:22	112:7 114:4	345:13 383:14
<b>separate</b> 52:17	<b>settings</b> 131:17	307:9 311:3	153:20 165:17	<b>signal</b> 180:11
191:11 204:21	131:19,22	313:18 316:6	167:11 172:13	194:20 203:13
328:10	132:3,19	317:15 318:3	184:16,21	204:19 256:4
<b>separated</b> 52:17	173:17,20	319:16 321:22	186:4,18 189:8	257:12 282:4,4
149:22	178:11 179:2	325:1 327:16	222:14 223:9	282:9 308:1,6
<b>separately</b> 158:6	179:22 360:11	328:1 347:7	228:3 235:10	308:11 311:6,6
217:21 304:8	<b>seven</b> 34:8 37:22	350:16 352:20	247:19 274:13	313:1 319:16
<b>separation</b> 66:3	40:19 44:13	354:14 359:1	311:6 328:15	321:7,7,18
67:16	89:4,9 100:17	364:19 368:1	336:14 347:16	324:11,18,22
<b>separations</b>	109:14 112:14	374:12 382:12	378:14 381:1	325:5,16,22
70:22	142:21 190:8	384:9	<b>showed</b> 19:8	327:4 333:21
<b>sepsis</b> 103:3	228:9 231:6	<b>shortage</b> 288:12	65:7,16 67:1	336:4 343:17
<b>sequential</b>	240:15 254:19	<b>shortages</b> 291:7	67:16 68:20	346:3 350:10
265:16	255:8 261:7,7	<b>shorten</b> 29:21	76:16,18 79:20	364:20 373:21
<b>serious</b> 21:6	271:5 276:17	58:13 332:21	96:14 97:13	<b>signaling</b> 262:18
30:10 37:9	279:2 281:6	<b>shortened</b> 33:13	106:8,12 112:9	263:22
38:5 41:13	292:5 307:10	58:1 298:3	112:16 165:13	<b>signals</b> 165:14
58:12 80:1,3	313:8 317:4	<b>shorter</b> 78:2	182:4 225:6	165:18 353:2
119:15,22	320:3 328:2	143:12	234:15 241:18	366:21 367:7
136:5,13	359:4 382:13	<b>shortly</b> 34:5	241:21 257:10	383:7
145:12 148:15	<b>seven-day</b>	39:9	265:18 271:21	<b>significance</b>
149:13 150:1,4	100:20 201:16	<b>short-term</b>	<b>showing</b> 28:21	50:9 54:6
150:6,17	271:9 326:1	19:19,22	108:19 123:20	77:18 101:17
152:16 153:13	<b>severe</b> 27:12	156:15 180:5	228:12 236:16	278:3 316:21
153:16 154:2	32:4 34:16,18	183:13 195:5,7	265:1 308:22	318:11
156:6,13	61:21 73:5	201:9,12	320:2	<b>significant</b> 18:22
165:15 178:22	315:10 320:7	205:21 206:4	<b>shown</b> 25:2	27:1 29:6 48:8
192:7 273:11	<b>severity</b> 264:16	277:18 279:18	29:20 66:2	48:12 50:12
274:1 360:9	<b>sex</b> 54:21 171:14	280:3,19	67:11,20 70:1	53:22 54:3,8
<b>served</b> 287:7	<b>shape</b> 215:14	281:10,20	82:7,12 102:2	55:17 57:1,6
<b>serves</b> 87:9	229:11 249:18	310:16 311:1	115:3 142:19	58:15 59:11
<b>Service</b> 3:15	<b>share</b> 25:11 35:6	311:18 312:5	143:14 146:15	63:7,14 64:8
<b>services</b> 12:5	<b>sharp</b> 330:11	315:17 318:22	201:10 223:5	68:20,22 69:9
<b>session</b> 271:13	<b>sharply</b> 133:15	319:9,19	271:20 293:20	70:20 74:6
334:7	<b>shed</b> 184:5	321:17 322:1	297:8 306:16	84:2 91:4
<b>sessions</b> 211:7	<b>shift</b> 240:3	324:11 325:6	341:12	97:19 98:17
<b>set</b> 24:1 92:16	298:18 322:6	331:13 348:17	<b>shows</b> 66:3 70:3	124:4,9 140:13
133:4,8 155:13	<b>shifting</b> 53:1	350:10 351:3	70:6 79:1	140:18 141:15

167:11,14,21	<b>simple</b> 343:3	255:21 281:18	268:4 286:8,12	<b>sorry</b> 124:20
168:2,7,9,11	<b>simply</b> 93:1	375:19	286:14 307:11	195:17 199:21
169:19 170:4	128:3 234:18	<b>skewed</b> 201:5	308:4 313:16	207:20 209:13
170:11 171:2,9	254:2 365:1	<b>skewing</b> 187:17	324:18 328:3	232:2 254:21
171:14,15	<b>single</b> 43:22	<b>skills</b> 179:2	331:14 340:3	255:3 290:3,4
172:7 186:18	61:14 77:7	360:11	349:13,14	304:18 353:11
197:15 214:12	81:7 206:16	<b>skin</b> 170:2 171:3	350:14 351:4	369:15
214:18 216:21	234:2 251:3	<b>skirting</b> 277:20	382:14 383:20	<b>sort</b> 20:3 203:18
229:7 265:19	254:5 271:15	<b>slam</b> 343:16,18	384:12,12	211:18,20
282:6 286:4	272:4 274:11	<b>sleeping</b> 122:15	<b>smaller</b> 86:15	216:10 253:21
288:3,15	282:5 366:1	<b>sleeve</b> 330:21	133:6 146:12	269:10 285:16
291:12 296:13	368:18 369:4	<b>slide</b> 97:13	147:18	338:7 355:17
299:6 308:21	383:6	106:12 117:11	<b>smokers</b> 111:9	358:15 383:12
309:19 314:17	<b>sit</b> 60:21	124:22 131:7	149:10	<b>sorts</b> 111:3
325:17 326:10	<b>site</b> 14:18 34:3	139:21 145:20	<b>Smoking</b> 111:4	361:22
326:17 333:3	83:15 231:8	146:15 147:15	<b>smooth</b> 29:12	<b>sought</b> 81:11
333:21 334:11	234:2,6,7	182:4 191:1,13	207:12	<b>sound</b> 201:1
334:15,17	356:2	199:9 202:1,9	<b>social</b> 43:10	<b>sounded</b> 112:17
341:10,12	<b>sites</b> 38:4 65:21	214:21 225:14	<b>socioeconomic</b>	<b>source</b> 81:17
345:3,21 346:4	198:5 231:3,6	228:5,8,12	23:17	118:8 120:7
<b>significantly</b>	231:12,14,17	231:2,13,16	<b>solely</b> 18:9 43:5	<b>South</b> 9:9
31:12 32:19	234:14 266:20	233:4,7,14	129:9 139:11	<b>Soviet</b> 231:15,19
71:16 86:21	268:5 273:7,11	236:16 241:18	<b>solicit</b> 323:7	<b>so-called</b> 31:22
186:21 265:21	273:16,21	247:18 248:6	<b>solicitation</b>	<b>space</b> 91:18
<b>signs</b> 28:4 31:15	<b>sitting</b> 129:12	254:21,22	311:10	<b>spanned</b> 261:6
<b>silence</b> 7:20	332:14 347:21	257:17 295:11	<b>solid</b> 42:3,16	<b>spans</b> 246:2
<b>Silver</b> 1:20	<b>situation</b> 181:15	311:15 360:7	135:16 138:18	<b>Spartanburg</b>
<b>similar</b> 23:11	290:17 293:19	<b>slides</b> 117:11	289:1,2	9:9
37:13 52:3	294:13 298:7	118:2 121:21	<b>solids</b> 40:2 52:14	<b>speak</b> 6:22 7:10
54:17 55:18	323:3 347:3	193:14	246:5	8:16 92:9
56:2 57:2,18	372:2	<b>slightly</b> 51:5	<b>solids-in</b> 112:7	134:4 213:14
96:14 143:2	<b>situations</b>	81:22 199:15	<b>solids-in/solid...</b>	264:5 273:2
144:11 146:12	218:17	224:3 334:20	112:11	331:19
146:19 149:16	<b>six</b> 66:6 78:17	<b>slim</b> 358:11	<b>solids-out</b> 112:7	<b>speaker</b> 13:21
157:8 161:5	101:10 137:10	<b>slippery</b> 325:3	<b>somebody</b> 288:7	121:13
164:20 179:5	142:21 143:17	<b>small</b> 8:8 13:11	342:15	<b>speakers</b> 10:16
192:11 200:12	158:14,16,19	16:20 17:21	<b>somewhat</b> 54:17	<b>speaking</b> 13:3
201:2 202:3	163:11 186:17	40:6 45:2 67:3	81:8 97:18	<b>speaks</b> 233:4
218:5 220:21	260:7 279:3	70:4 71:8,17	112:1 114:20	<b>special</b> 11:7 12:1
230:3,7 266:20	282:19 292:5	80:3 126:12,21	164:3 201:5	12:9,15 134:19
280:11 313:17	330:1 352:7	129:1,5,14	202:18,22	148:6,14
320:11 344:1	372:20 381:12	135:10 137:13	224:10 234:19	<b>specialist</b> 118:22
360:14	<b>sixties</b> 317:8	145:17 159:3	250:22 251:2	301:12
<b>similarities</b>	<b>six-month</b>	164:2 199:1,8	258:15 310:15	<b>specialists</b> 364:8
109:9	168:15,18	199:16 221:11	<b>Sonia</b> 4:19	<b>specialized</b>
<b>similarly</b> 68:22	<b>six-plus</b> 84:3	222:19 223:3	326:16	177:1,5 179:1
76:8 145:5	<b>six-week</b> 83:11	225:8 227:11	<b>soon</b> 128:4	360:10
157:20 215:16	<b>size</b> 195:2 213:2	232:4,9 265:7	272:18	<b>specializing</b>

81:14 <b>specially</b> 178:2,6 <b>specialties</b> 176:11 <b>species</b> 166:15 168:8 <b>specific</b> 18:14 81:21 87:9 88:22 113:6 150:12 165:14 173:6 192:15 196:8 270:20 359:7 383:14 385:3,17 <b>specifically</b> 89:2 215:11 219:18 222:14 230:17 259:4 284:12 353:8 365:8 <b>specifics</b> 359:1 359:12 <b>specified</b> 357:15 <b>specifies</b> 180:19 <b>specify</b> 98:8 285:5 299:22 304:22 <b>spectrum</b> 5:13 26:18 213:20 249:5 <b>speculative</b> 270:2 <b>spend</b> 284:2 <b>spent</b> 287:14 <b>spikes</b> 279:4,17 280:5 281:2 <b>spin</b> 240:18 <b>spinal</b> 221:15 <b>spirit</b> 7:2 <b>split</b> 368:11 <b>sponsor</b> 16:5,6 17:2,10 18:3 19:3 20:8 92:2 92:6,8 130:18 136:2,7,11,17 137:6,10 138:1 139:4 173:2 179:10 182:16 182:20 183:6	185:18 186:6 187:1,8,21 188:19 193:14 196:14 197:4 197:13 202:15 205:15 206:11 207:13 212:1 212:14,16 214:6,9 227:18 234:1 235:14 236:4 261:12 263:11,17 322:17 337:2 343:2 348:19 354:17 358:16 377:18 380:12 381:9 <b>sponsors</b> 10:16 <b>sponsor's</b> 16:7 16:12 135:8 136:16 152:2 188:4 193:4 194:10 198:19 199:12,13 219:14 <b>spouses</b> 12:19 <b>Spring</b> 1:20 <b>squamous</b> 159:8 <b>St</b> 4:18 26:4 118:18 <b>stability</b> 321:8 <b>stacked</b> 290:14 <b>staff</b> 287:7 289:19 <b>stages</b> 265:17 <b>stand</b> 7:18 339:8 <b>standard</b> 29:17 68:13 120:2 229:5 277:3,7 <b>standardized</b> 39:15 60:2 94:7,8 205:16 206:20 <b>standing</b> 290:10 <b>standpoint</b> 116:1 249:16 259:22 288:17 296:4 301:19	316:12 376:18 <b>stands</b> 305:6 377:18 <b>Stanford</b> 2:13 9:3 99:6 <b>start</b> 6:11 8:13 35:11 120:10 134:2 136:13 231:4 272:19 305:18 328:20 329:10 331:16 338:21,22 342:7 350:2 351:10 352:17 370:15 <b>started</b> 16:12 134:1 174:1 181:13 367:21 <b>starting</b> 48:3 366:22 <b>starts</b> 237:10 <b>state</b> 3:6 9:5 26:16 89:2 234:10 300:18 305:17 306:18 328:18 329:21 351:8,22 370:14 371:9 <b>stated</b> 68:9 174:12 379:2 <b>statement</b> 10:18 10:20 15:2 131:2 243:22 299:22 305:3 <b>statements</b> 6:8 <b>states</b> 89:13 108:11,15 218:20 232:11 232:13 268:1,3 364:22 365:1 <b>stats</b> 187:15 <b>statistical</b> 50:9 54:5 308:18 309:18 316:21 318:11 <b>statistically</b> 18:22 48:7 50:12 53:21	54:3,8 55:16 57:1,5 59:11 97:19 98:16 124:3,9 140:18 141:14 169:19 170:4 171:2,8 171:13,15 249:21 308:21 309:19 324:12 325:16 326:9 334:10 <b>statistician</b> 26:8 118:22 259:19 259:22 <b>statisticians</b> 261:21 <b>status</b> 11:12 160:17 162:2 238:1 <b>stay</b> 27:8 29:22 30:12 31:11 32:13,14 33:14 41:5,7 43:3,15 46:3 48:15 49:3,8 55:14 57:22 59:13 100:12 101:10 143:10,12,15 144:1 184:9 190:8 193:8 216:18 227:4 239:22 240:15 241:6,10 276:12,15 285:9 288:19 298:4 340:13 345:22 <b>staying</b> 291:21 <b>stays</b> 90:16,21 181:14 242:14 260:3 <b>step</b> 174:17 265:17 317:22 <b>steps</b> 56:10 174:12 265:8 <b>stomach</b> 126:19 128:14 129:12 129:13 286:13	<b>stool</b> 28:6 42:9 <b>stop</b> 345:10 <b>stopped</b> 282:14 <b>story</b> 366:3 <b>straight</b> 326:4 <b>straightforward</b> 19:5 117:13 380:13 <b>strategic</b> 173:5 <b>strategies</b> 173:12,15 <b>strategy</b> 33:17 108:7 192:12 218:2,5 331:21 <b>stratification</b> 379:19 <b>strengths</b> 133:4 <b>stress</b> 28:12,19 347:1 <b>stresses</b> 317:11 <b>stressful</b> 347:3,5 <b>strict</b> 89:18 315:6 341:21 <b>stricter</b> 354:9 <b>strictly</b> 224:1 256:1 <b>strictureplasty</b> 314:6 <b>stride</b> 340:2 <b>strides</b> 339:21 339:22 <b>striking</b> 312:8 <b>strikingly</b> 156:8 <b>stringent</b> 360:18 <b>stroke</b> 224:13 <b>strong</b> 94:19 321:7 344:6,8 354:15 <b>stronger</b> 216:3 <b>strongly</b> 6:17 <b>struck</b> 343:2 <b>structure</b> 208:11 239:10 379:5 <b>structured</b> 108:13 <b>stuck</b> 239:12 323:15 <b>studied</b> 22:9
---	---	---	--	--

33:9 61:22	165:16 166:1,2	42:20 43:1,2	165:9,12	379:1,7 380:5
187:3 335:15	166:5,6,7,8,14	44:5 45:4,5,14	168:15,19	380:12,16
<b>studies</b> 17:8,18	166:17,22	45:14,17,22	169:17 184:13	383:6
18:17 19:2,9	167:1,8,9	46:1,11 48:4,5	184:14 185:15	<b>study's</b> 64:3
23:7 30:22	168:6,8,13	48:13,19 49:5	186:4,7,7,7,11	72:17
33:14 38:13	169:1,4,11	50:1,9 51:8,14	186:17 187:2,2	<b>subacute</b> 166:16
42:22 44:6	172:4,5,6,8,10	57:3,4,9 58:3	187:8,11,13	<b>subchronic</b>
45:9 46:6	172:13 183:22	61:3,15,17	191:3,15,21	166:16
49:11 50:18	184:21 186:14	63:17 65:6,21	192:3,12,16,17	<b>subcutis</b> 170:2
51:1 53:16,17	186:16,17	66:2,12,14,22	192:17,20,20	171:4
54:1,5,7,16	194:21 196:1	67:14 68:1	192:20,22	<b>subgroup</b> 23:5,8
55:1,16,19,22	201:10 204:4	69:13,19 71:11	193:9 195:3,11	137:22 215:12
56:3,4,8,21	208:20 209:5,6	72:7,9 73:1,6,8	196:18,18	<b>subissue</b> 230:15
57:8,12,17,18	210:14 223:22	74:1,11,16,19	197:3,6,9,12	<b>subject</b> 11:9
58:1,5 59:6,8	225:16 228:19	75:22 77:8	197:15 203:14	<b>subjected</b> 65:3
60:7 61:10	231:1 232:13	82:15 83:11	206:2,5,5	<b>subjective</b>
63:16 64:12	236:4 238:22	91:7 93:5	207:13 208:7,8	299:13
66:16,18 67:1	245:15,22	97:11 98:6,7	209:10 217:19	<b>subjects</b> 74:2,4
67:10 69:15	247:20,22	98:14,14	218:11,12	74:18 110:19
71:22 72:6,22	248:7,15 255:5	100:15,16	220:6 222:14	158:10,11
74:17,21 75:3	256:10 257:6	109:15 110:7	222:16 224:1	160:8,12 164:9
76:2,10,15	257:13,13	110:13 111:7	225:2 228:22	187:13 231:21
77:10 78:3,13	259:11 261:4	115:14 118:11	230:20,21	<b>submission</b>
78:16,17 79:9	266:5 267:5	119:4 120:9	232:10 233:9	32:10 137:22
82:20 83:2,15	270:8,8 280:19	123:21 131:9	255:12,16	147:11 148:10
91:8 94:2 98:5	280:20 281:5	132:11 136:15	257:11,17	179:11 184:19
102:10 109:5	281:10 282:6	136:15 137:15	263:1,12,13	<b>submitted</b> 17:8
110:9 112:8	283:11 293:5	138:3,5,12,22	264:15 267:14	23:22 136:2,7
114:7,9 117:7	293:10 294:4,6	139:3,20,21	268:10,20	136:11,17
117:8 121:5	295:8 296:19	140:7,8,15,16	271:21 272:5,7	137:6 141:1
126:9 128:18	304:16 305:1	140:22 141:4	273:13 274:5	179:13 180:13
128:21 131:3,6	308:3,4 311:4	141:13 142:8	282:5,12,19	183:5 184:1
131:12,17	320:20 322:21	142:22 143:1,1	283:5,8,9,10	196:14 293:4
132:1,7,17	325:6 345:17	143:10,15	283:12 292:5	304:16 382:7
137:5,11,12,16	346:2 347:16	148:18 152:1,5	296:10 310:12	<b>submitting</b>
137:19 138:21	348:17 350:11	152:8 153:8,10	315:17,21	14:21
139:9 141:19	361:1 362:5,6	153:22 154:10	316:9 318:8	<b>subsequent</b> 44:9
142:7,13,20	363:6,8 366:4	155:17,21	319:21 320:1	65:16 138:8
143:11,16	366:19 372:16	156:2,4,8	320:16,16	254:17
144:7 147:8,14	372:19 374:3,4	157:8 158:5,6	324:11,12	<b>substantial</b> 32:5
147:16 148:21	381:1 382:7	158:8,17,18	326:17,22	41:7 288:5
151:3 152:18	385:9,12,20	159:11,12,17	327:5 335:3,7	303:8
153:2,3,6,7,12	<b>study</b> 14:12	159:18 160:3,8	336:13 337:14	<b>substantially</b>
154:12 155:15	22:20 23:13,13	160:12,18,20	346:16,20	200:2,19
156:3,8,21	23:14,22 24:1	161:6,6,8,15	349:5,8 353:3	222:22 256:17
157:5,11,12,14	24:3,4,12	161:18,22,22	360:4 374:19	298:4
159:8,10,13,15	25:18 35:13	162:15 163:4	375:7 376:22	<b>subtle</b> 113:5
159:20 162:13	37:13 38:6	163:19 164:18	377:2 378:2	<b>subtract</b> 191:4

<b>sub-analysis</b> 214:9	170:12	326:3,11	111:22 128:3,8	251:22
<b>success</b> 175:9	<b>summary</b> 25:20	336:18 339:16	135:11,15	<b>suspect</b> 215:12
182:2	35:15 59:7	342:12 349:9	137:15,21	312:14,15
<b>successful</b> 98:5	75:6 77:6 84:8	354:1 356:13	138:2,8,15	363:16
<b>sudden</b> 224:15	90:12 143:18	374:4	139:10,13	<b>sustained</b> 162:6
<b>suddenly</b> 275:11	146:18 156:5	<b>surfaced</b> 196:4	141:17 145:3,4	<b>SUZANNE</b> 2:14
<b>suffer</b> 31:4	161:9,19	197:1	162:8 181:7	<b>symptom</b> 342:19
<b>suffered</b> 62:22	164:22 211:19	<b>surgeon</b> 18:10	213:5,8,9,10	<b>symptoms</b> 41:11
<b>suffers</b> 300:15	330:18 381:12	26:5 27:17	221:5,15	58:8 61:21
300:21	<b>Sunshine</b> 7:4	38:8 43:6	226:20 245:15	62:14 63:21
<b>sufficient</b> 180:6	<b>superior</b> 113:7	83:10,20 94:11	256:12 276:12	72:13 73:7
183:14 246:21	<b>superiority</b>	139:13 205:12	291:15 296:22	147:7 240:20
284:13 340:17	23:15	221:1 226:19	297:6 298:17	<b>syncopal</b> 162:7
<b>sufficiently</b>	<b>supplement</b>	273:5 278:14	317:10 328:4	<b>syncope</b> 164:8
166:5	47:16	293:22 332:2	335:10,11	<b>Syracuse</b> 3:7 9:7
<b>suggest</b> 76:22	<b>supply</b> 176:17	340:9 346:10	336:17 338:12	<b>system</b> 21:8
156:12 182:15	176:19 183:7	<b>surgeons</b> 27:10	339:16 347:1	28:17 29:11
184:2 247:1	359:17	32:7 44:4	347:12,14	34:18 36:20
269:21 270:2	<b>support</b> 24:16	103:8 192:9	357:20 366:2	41:9 87:3
271:17 323:9	31:16,17 40:22	217:7 218:2	375:8 376:16	90:11 95:3
366:7 372:14	45:12 54:1	221:3 235:15	376:17 382:15	166:9,10,11,11
379:10	84:16 115:12	244:20 245:22	<b>surgical</b> 25:11	177:10 180:19
<b>suggested</b> 69:12	146:7 182:7	261:20 262:7	26:19 27:5	181:16 208:9
74:7 83:22	250:5 293:10	273:8 285:22	28:12,13 29:1	347:4,4,6
253:14 264:12	295:7 299:15	286:7 289:15	30:19 33:22	<b>systematic</b> 183:8
374:18	302:19 383:4	289:15 297:6	34:2 37:10	259:11 318:2
<b>suggesting</b> 66:6	<b>supported</b> 53:15	297:22 300:10	45:13 92:20	<b>systemic</b> 135:4
94:2 143:5	54:16 59:22	348:2,11,13	93:16 94:8	208:17
227:14 345:5	<b>supporting</b> 35:8	365:5	104:19 213:18	<b>systems</b> 23:17
366:16 372:22	179:14	<b>surgeon's</b> 93:2	214:3 221:12	87:22 88:4
<b>suggestion</b>	<b>supportive</b> 56:3	300:3	301:7	99:20 174:21
322:18 344:7	<b>suppose</b> 235:9	<b>surgeries</b> 226:14	<b>surprise</b> 330:21	175:3,5 176:13
366:5	<b>suppositories</b>	227:16 288:9	<b>surprised</b> 205:7	176:14,17
<b>suggests</b> 30:7	228:21	303:6 314:15	317:9 359:2	177:17,17
155:11 159:4	<b>suppression</b>	356:16 379:22	<b>surrogate</b> 175:8	178:2 359:21
241:5 309:15	323:19	<b>surgery</b> 2:19	343:4	363:16
309:21	<b>sure</b> 87:4 92:9	3:17 6:6 8:8	<b>surrounding</b>	
<b>sum</b> 47:12 271:1	95:5 100:2	13:11 16:21	81:4	<b>T</b>
<b>summarize</b>	102:4 113:9	17:22 18:7	<b>surveillance</b> 4:7	<b>T</b> 4:14 211:1
157:6 165:11	115:7 191:13	26:15 27:15,19	4:11 10:5,7	<b>table</b> 8:14 15:3
172:2	199:1 201:20	30:6,9 31:1	263:5 269:20	139:16 140:3
<b>summarized</b>	202:2 206:15	40:20 41:3	270:3 315:7	141:6,16,20
74:13	206:17 219:11	43:17 45:21	353:22	142:4,7 143:9
<b>summarizes</b>	225:13 227:9	46:11 50:3	<b>survey</b> 235:15	144:17 151:1
139:16 141:16	230:14 233:3	52:2,5,16	<b>surveys</b> 175:16	153:5 154:20
142:4 143:9	244:15 263:8	79:12 93:21	<b>survival</b> 203:17	155:2 162:20
144:17 145:20	269:1 278:20	95:21 106:18	264:1	170:12 199:11
	291:4 294:21	107:15 111:19	<b>survivorship</b>	201:21 202:1,5

223:4 281:16 300:10 <b>Taiwan</b> 268:9 <b>take</b> 7:5,6 20:4 88:9 93:14 100:17 102:9 113:11 115:4 130:1 133:13 189:20 210:16 249:2 271:12 285:16 312:14 312:21 317:6 317:22 318:7,9 330:5,7,9 332:8 335:22 346:13 358:17 375:20 385:13 <b>taken</b> 136:9 210:22 337:7 <b>takes</b> 260:7 <b>Talamini</b> 3:16 10:1,1 92:11 92:12,12 93:13 192:8,9 207:1 207:6 217:14 217:18 244:14 244:15 281:18 285:20,21 286:21 288:20 289:13,13 297:21 298:10 298:11,15 303:11,13,14 305:19,20,20 310:4,5 329:11 329:12,12 331:17,19 351:20,20 365:9,10 370:15,16,16 375:3,4 <b>Talamini's</b> 303:6 <b>talk</b> 16:15 133:17 172:20 193:17 277:19 278:4 320:9,14 322:9 350:1	<b>talked</b> 268:15 355:16 <b>talking</b> 61:9 133:18 194:4 232:12 265:7 284:19,19,20 285:1,11 287:1 288:4 291:9,11 291:13 295:20 301:1,4 316:7 320:14 322:1 322:10 367:21 373:9,13 374:2 378:2 <b>TAMAL</b> 3:21 <b>target</b> 145:2 168:7 172:7 177:18 210:15 354:4 <b>targeted</b> 175:19 180:17 <b>targets</b> 37:9 <b>taught</b> 27:18 <b>teaching</b> 13:3 <b>team</b> 10:3,8 81:13 134:2,7 148:7 290:8,9 <b>tease</b> 294:18 <b>Techner</b> 5:14 23:19 25:12 34:6 35:1,4,5 83:19 84:12 93:15 94:4,5,5 94:16 95:5 97:2,10,21 98:2,11 100:2 102:6 104:5,8 104:10 107:1 107:12,22 111:13 113:2,9 122:7,8 123:5 123:8,11,14 125:9 126:4 127:1 128:16 129:19 214:17 214:20 216:6 216:16 217:2 217:11 218:6	219:11,22 229:2 230:5 233:5 236:9,9 241:16 245:18 246:10 248:2,8 248:11,18 249:11 253:21 254:1,8 257:16 258:5 261:5 272:10,19 274:14 275:12 277:2 <b>technique</b> 27:5 97:12 218:13 <b>techniques</b> 214:3 294:5 335:6 <b>telephone</b> 83:7 151:5,7 <b>tell</b> 127:10 197:13 207:22 230:11 244:11 245:21 261:12 273:6 276:10 338:13 342:17 350:4 <b>temporary</b> 2:16 3:2 92:14 <b>tend</b> 29:4 258:15 <b>tendency</b> 105:20 216:1 <b>tens</b> 315:4 <b>tenth</b> 63:11 <b>teratogenic</b> 172:16 <b>term</b> 78:2 85:4 109:4 180:11 181:2 183:10 197:8 279:6 280:22 281:22 307:9 311:3 317:15,22 318:3 319:16 323:8 325:1 327:17 328:1 344:4 347:8 350:16 352:20 353:9 354:14	364:19 368:1 372:20 374:13 374:14 382:12 384:10 385:11 <b>terms</b> 110:14,21 117:20 122:4 126:20 132:5 174:13 209:2 212:3 214:5 219:14 223:9 224:6,18,22 225:3,9,11 234:21 249:9 253:10 259:20 260:15 269:18 286:2,3 293:18 298:20 301:21 309:9 310:11 313:5 333:10 348:6 349:13 349:14 350:7 377:3 <b>terrific</b> 92:17 <b>test</b> 169:2,3,3,8 170:17 308:19 309:18 363:7,8 <b>tested</b> 140:12 166:4,21 167:5 167:16,19 168:9,22 169:5 170:6 209:7 319:22 <b>testimony</b> 13:2 <b>testing</b> 178:15 178:16 180:12 <b>tests</b> 169:8 259:6 <b>thank</b> 8:1 10:14 16:10 20:22 26:13 60:17 61:4,7 78:8 92:4 93:13 99:5 110:4 122:3 127:16 132:4 172:17 172:19 212:11 213:1 214:7,17 223:13 242:22 255:19 307:4	<b>thanks</b> 133:20 148:7,8,11 301:9 386:1 <b>theory</b> 319:12 <b>therapies</b> 135:21 318:20 319:2 <b>therapy</b> 17:4 24:6 136:6 148:4 173:22 181:12 204:14 205:5 319:1,10 <b>They'd</b> 63:1 <b>thin</b> 375:5 <b>thing</b> 103:4 105:4,11 111:14 191:12 215:16 238:15 242:6 243:21 260:18 280:9 281:1 286:11 287:5 301:4 303:14 309:10 324:17,20 325:15 332:10 332:14 350:6 361:22 <b>things</b> 78:5 99:2 102:9 111:3 190:19 215:1 236:18,22 261:10,18,18 277:22 278:16 278:18 289:17 291:4 294:3 324:9,16 333:10 340:10 345:3,21 346:12 347:19 356:14 357:3 359:12 367:3 <b>think</b> 19:4 70:2 79:4 85:15 94:16 95:16 96:12 97:12 98:14 99:9 100:2,5 101:15 102:6,8 103:6 104:20 105:12
--	--	--	--	---

108:1,6 111:14	286:1 288:17	359:17 360:3	320:15,21,22	154:20 155:2,6
113:11 115:13	289:16 291:12	360:15 361:3	324:9 325:22	155:8 158:12
121:8 122:1,10	293:14,22	362:3 363:10	328:9 346:12	160:2 163:9
122:17 124:2	294:3,17,22	363:22 364:12	353:2 372:19	177:1 187:4
124:13 129:8	295:4,7 296:9	364:21 365:3,6	383:7	189:7,13 190:1
133:8 182:6	296:10,12	365:16 366:21	<b>three-compon...</b>	190:10 193:13
183:4,7 186:10	297:13 298:15	367:5,8,18	41:22	196:1 199:4
190:18 191:5,9	298:17 299:5	369:1,6,8	<b>Three-quarters</b>	207:22 212:18
193:12,13	299:16,18,22	370:3,4,8,11	83:7	233:2 237:9
194:6,9 195:13	300:13 301:13	372:4 374:6,13	<b>three-week</b>	242:7 243:5,9
195:19,20	301:16,19,21	375:6 376:2	72:18	246:3 251:4,8
197:12,15	302:18,20	378:12 379:4	<b>threshold</b> 95:10	251:12 260:2,5
198:22 199:6	303:20 305:4	379:17 380:12	218:22	260:8 262:4
199:16 200:20	308:1,3,5,11	380:14	<b>thromboembo...</b>	270:12 272:6
202:1 203:3	310:7,14,19	<b>thinking</b> 131:20	102:21 345:20	273:14 274:2
204:8 205:10	311:7,16 312:3	203:21 205:19	<b>thrombosis</b>	274:15 275:2
206:12 211:10	312:6 313:6	228:2 259:21	319:8	279:15,21
212:4 214:22	314:20 315:9	269:11 291:8	<b>throughput</b>	280:3 283:4
215:3 218:1,6	315:16 316:1,3	377:12	31:21	284:18 286:17
218:21 219:22	316:22 317:13	<b>third</b> 71:21	<b>throw</b> 343:19	287:14 288:19
220:2,5 222:2	318:13,21	137:7 243:21	<b>TIA</b> 224:14	295:18 296:1
222:17 223:16	319:5 322:14	262:2	<b>tied</b> 294:12	298:13,17
224:3 225:22	323:17 324:1,4	<b>Thirdly</b> 270:12	<b>ties</b> 194:18	299:2 303:9,13
226:8,13 227:1	325:15,19	<b>third-party</b>	<b>tight</b> 210:20	311:4 312:1
228:1 229:14	326:1,13 327:4	119:17	<b>time</b> 8:6 13:9	313:17,19
234:5 235:6,12	327:16 328:11	<b>thorough</b> 385:19	16:18 17:17	316:6,19 317:3
236:18 237:3,8	332:8,21 333:7	<b>thought</b> 94:19	18:7,8,20 30:8	340:1,12 343:7
237:16,19	333:11 334:6	205:12 245:13	31:2 42:2,16	358:22 369:6
239:15,17	335:8,10,18	265:9 269:9	42:17 43:5,6,8	375:20 377:11
240:2,20 242:1	336:2,3 337:3	324:3	43:18,22 46:22	379:1
242:6,17,19	337:4,5,13,18	<b>thoughts</b> 182:5	47:2 49:6	<b>times</b> 39:2 47:9
243:2 244:2,7	339:2,7,12,20	236:13,13	52:22 77:10	49:1 123:15,16
244:12 245:18	340:13,16,22	269:2	79:10 84:2	171:11 180:10
245:19 246:10	341:20 342:2	<b>thousands</b> 315:5	91:9 99:7	202:20 284:7
246:11 247:9	342:10 344:14	<b>three</b> 40:18,22	100:22 101:5	335:11 336:12
249:5,16,21	344:15,19,21	49:9 64:7	113:19 114:3	357:14 381:17
250:11 253:12	345:4 346:1,21	66:19 67:12	115:7 117:3	<b>timetable</b>
254:8 255:2,4	348:8,14,19	78:16 100:10	125:17 128:20	197:13
255:12 256:2	350:14,15	100:14 104:18	129:3 130:4,16	<b>time-to-event</b>
258:6,11 261:8	352:18,21	119:20 121:3	131:4,8,21	66:1 67:8
261:17 262:5	353:1,8,12	123:10 139:22	135:9 138:14	150:19 159:2
263:18 270:1	354:11,13,21	143:10 148:14	138:15 139:10	160:1 251:21
272:3,8,12,20	355:14,18,19	158:21 165:14	139:10,13,14	<b>time-to-fracture</b>
273:1,1 275:14	355:21 356:7,8	175:1 189:6	139:17,22	163:18
277:2 278:17	356:14,15,19	231:8 234:2	140:5 141:8,17	<b>tissues</b> 207:19
279:14 283:1	356:20 357:3,8	261:18 279:3	141:17,21	<b>titrate</b> 115:6,7
284:12,17	357:13,21	282:7,14	142:5,14 143:2	<b>Tmax</b> 135:5
285:3,7,18	358:4,19	295:21 315:1,8	143:4 150:22	<b>toast</b> 289:5

<b>tobacco</b> 75:12 75:13	40:7,15 63:4 73:22 78:19	133:20	97:16 100:19 100:20 103:16	201:3 214:15 235:1 302:6
<b>today</b> 7:6 10:22 16:12 17:5 19:10,16 21:1 21:2 22:16 24:16 25:8,22 27:20 35:6 44:1 61:8,9 63:15 84:16 85:16 134:9 144:7 212:5 218:10 227:2 244:17 269:1 310:15 330:19 350:18 355:11 374:8	100:17 137:14 137:21 144:13 149:12,21 153:12 154:14 157:17,20 164:18 186:17 190:7 199:20 200:17 221:15 231:21 232:7 232:15 268:1 296:19 297:1,7 319:21	<b>transcriber</b> 213:14 <b>transcript</b> 15:5 <b>transfer</b> 290:19 <b>transgender</b> 171:18 <b>transient</b> 27:13 135:14 <b>transit</b> 27:15 128:20 129:1,3 209:14 275:1 <b>translates</b> 32:15 326:1 <b>transportation</b> 43:10 <b>transspecies</b> 171:18 <b>trawled</b> 119:17 120:20 <b>treat</b> 33:18 47:21 216:13 221:4 253:12 253:17 254:3 337:17,22 <b>treated</b> 53:2 62:17 79:5 147:8 204:16 209:11 263:21 <b>treating</b> 219:16 219:20 276:8,9 276:21,21 332:18 <b>treatment</b> 32:21 33:11,17 39:5 42:12 44:18 46:18,22 47:11 50:5,14 51:16 52:3 53:20 54:11,19 55:7 55:20 57:14 58:13 59:3,7 60:5,8 62:14 64:15 70:19,22 72:20 73:12,15 77:4,12,17 79:2,18,21 82:2 96:15,16	106:21 119:8 121:18 123:1 138:6 145:7 149:7,15,20 150:10 151:20 153:21 154:8 154:14 157:2,7 157:16 158:1 158:20 159:15 160:6,18,20 161:8,17,21 162:14,16 163:11,13,21 164:1,6,12,17 164:20 165:9 187:15,19 189:22 199:18 200:8 204:13 215:10,11,15 229:15,18 230:7 235:5 243:15 250:1,7 262:8 264:21 265:15 266:18 267:1 284:10 331:11 351:2 362:7,16 381:20 383:17	309:4,8 323:20 333:22 364:18 372:5 373:1,6 373:14,14 375:14 376:18 377:9 378:12 379:16,18 383:22 385:15 <b>trials</b> 25:15 35:8 37:14 38:15 39:7,17 40:15 41:21 43:21 45:16 46:2,15 48:13,16 49:2 49:18 50:20 51:7 52:13 56:14 59:3 60:1,4 61:2 82:11 94:9 96:4 105:18 114:7 123:22 127:5,12 153:1 155:22 180:5 198:2 204:6 205:21 236:20 255:10 258:9 284:5 302:8 308:20 309:1,9 309:20 315:3 324:2 371:20 372:4,13 375:1 381:16
<b>today's</b> 6:15,18 11:2,17 12:14 13:5,13 14:15 15:8 24:13 61:13 64:2	<b>touch</b> 354:11 <b>tough</b> 335:19 336:3 <b>toxicity</b> 167:4 168:12,15,19 172:8 <b>toxicology</b> 166:17 168:6,8 168:13 172:6,8 172:13 208:20 210:14 <b>toxin-positive</b> 106:21 <b>TPN</b> 31:17 <b>tracings</b> 80:14 <b>tract</b> 32:2 103:2 116:17 138:16 138:17,19 139:17 143:2 143:21 146:8 208:13	<b>treat</b> 33:18 47:21 216:13 221:4 253:12 253:17 254:3 337:17,22 <b>treated</b> 53:2 62:17 79:5 147:8 204:16 209:11 263:21 <b>treating</b> 219:16 219:20 276:8,9 276:21,21 332:18 <b>treatment</b> 32:21 33:11,17 39:5 42:12 44:18 46:18,22 47:11 50:5,14 51:16 52:3 53:20 54:11,19 55:7 55:20 57:14 58:13 59:3,7 60:5,8 62:14 64:15 70:19,22 72:20 73:12,15 77:4,12,17 79:2,18,21 82:2 96:15,16	229:15,18 230:7 235:5 243:15 250:1,7 262:8 264:21 265:15 266:18 267:1 284:10 331:11 351:2 362:7,16 381:20 383:17	379:16,18 383:22 385:15 <b>trials</b> 25:15 35:8 37:14 38:15 39:7,17 40:15 41:21 43:21 45:16 46:2,15 48:13,16 49:2 49:18 50:20 51:7 52:13 56:14 59:3 60:1,4 61:2 82:11 94:9 96:4 105:18 114:7 123:22 127:5,12 153:1 155:22 180:5 198:2 204:6 205:21 236:20 255:10 258:9 284:5 302:8 308:20 309:1,9 309:20 315:3 324:2 371:20 372:4,13 375:1 381:16
<b>told</b> 267:12 274:14	<b>totality</b> 87:10 190:9 257:5 269:8 <b>touch</b> 354:11 <b>tough</b> 335:19 336:3 <b>toxicity</b> 167:4 168:12,15,19 172:8 <b>toxicology</b> 166:17 168:6,8 168:13 172:6,8 172:13 208:20 210:14 <b>toxin-positive</b> 106:21 <b>TPN</b> 31:17 <b>tracings</b> 80:14 <b>tract</b> 32:2 103:2 116:17 138:16 138:17,19 139:17 143:2 143:21 146:8 208:13	<b>treat</b> 33:18 47:21 216:13 221:4 253:12 253:17 254:3 337:17,22 <b>treated</b> 53:2 62:17 79:5 147:8 204:16 209:11 263:21 <b>treating</b> 219:16 219:20 276:8,9 276:21,21 332:18 <b>treatment</b> 32:21 33:11,17 39:5 42:12 44:18 46:18,22 47:11 50:5,14 51:16 52:3 53:20 54:11,19 55:7 55:20 57:14 58:13 59:3,7 60:5,8 62:14 64:15 70:19,22 72:20 73:12,15 77:4,12,17 79:2,18,21 82:2 96:15,16	<b>treatments</b> 227:13 <b>treatment-em...</b> 79:13 82:19 146:10,13,21 <b>trend</b> 54:4 57:3 103:13 169:19 170:4,17 320:12 <b>trending</b> 124:11 <b>trends</b> 54:17 105:15 <b>trial</b> 24:5 39:4 42:19 44:4 46:4 61:15 63:19 65:22 72:19 76:1 97:8 140:4	114:7 123:22 127:5,12 153:1 155:22 180:5 198:2 204:6 205:21 236:20 255:10 258:9 284:5 302:8 308:20 309:1,9 309:20 315:3 324:2 371:20 372:4,13 375:1 381:16
<b>tolerance</b> 27:16 246:13 289:3	<b>totality</b> 87:10 190:9 257:5 269:8 <b>touch</b> 354:11 <b>tough</b> 335:19 336:3 <b>toxicity</b> 167:4 168:12,15,19 172:8 <b>toxicology</b> 166:17 168:6,8 168:13 172:6,8 172:13 208:20 210:14 <b>toxin-positive</b> 106:21 <b>TPN</b> 31:17 <b>tracings</b> 80:14 <b>tract</b> 32:2 103:2 116:17 138:16 138:17,19 139:17 143:2 143:21 146:8 208:13	<b>treat</b> 33:18 47:21 216:13 221:4 253:12 253:17 254:3 337:17,22 <b>treated</b> 53:2 62:17 79:5 147:8 204:16 209:11 263:21 <b>treating</b> 219:16 219:20 276:8,9 276:21,21 332:18 <b>treatment</b> 32:21 33:11,17 39:5 42:12 44:18 46:18,22 47:11 50:5,14 51:16 52:3 53:20 54:11,19 55:7 55:20 57:14 58:13 59:3,7 60:5,8 62:14 64:15 70:19,22 72:20 73:12,15 77:4,12,17 79:2,18,21 82:2 96:15,16	<b>treatments</b> 227:13 <b>treatment-em...</b> 79:13 82:19 146:10,13,21 <b>trend</b> 54:4 57:3 103:13 169:19 170:4,17 320:12 <b>trending</b> 124:11 <b>trends</b> 54:17 105:15 <b>trial</b> 24:5 39:4 42:19 44:4 46:4 61:15 63:19 65:22 72:19 76:1 97:8 140:4	<b>tried</b> 103:19 105:14 189:8 283:2 <b>trigger</b> 276:13 <b>triggers</b> 372:14 <b>trouble</b> 312:21 321:14,21 <b>troubled</b> 336:21 337:16 338:6 <b>troubling</b> 290:17 <b>true</b> 99:11 245:2 245:6 282:20 332:16 342:15
<b>tolerate</b> 135:16 246:21 247:4 334:16	<b>totality</b> 87:10 190:9 257:5 269:8 <b>touch</b> 354:11 <b>tough</b> 335:19 336:3 <b>toxicity</b> 167:4 168:12,15,19 172:8 <b>toxicology</b> 166:17 168:6,8 168:13 172:6,8 172:13 208:20 210:14 <b>toxin-positive</b> 106:21 <b>TPN</b> 31:17 <b>tracings</b> 80:14 <b>tract</b> 32:2 103:2 116:17 138:16 138:17,19 139:17 143:2 143:21 146:8 208:13	<b>treat</b> 33:18 47:21 216:13 221:4 253:12 253:17 254:3 337:17,22 <b>treated</b> 53:2 62:17 79:5 147:8 204:16 209:11 263:21 <b>treating</b> 219:16 219:20 276:8,9 276:21,21 332:18 <b>treatment</b> 32:21 33:11,17 39:5 42:12 44:18 46:18,22 47:11 50:5,14 51:16 52:3 53:20 54:11,19 55:7 55:20 57:14 58:13 59:3,7 60:5,8 62:14 64:15 70:19,22 72:20 73:12,15 77:4,12,17 79:2,18,21 82:2 96:15,16	<b>treatments</b> 227:13 <b>treatment-em...</b> 79:13 82:19 146:10,13,21 <b>trend</b> 54:4 57:3 103:13 169:19 170:4,17 320:12 <b>trending</b> 124:11 <b>trends</b> 54:17 105:15 <b>trial</b> 24:5 39:4 42:19 44:4 46:4 61:15 63:19 65:22 72:19 76:1 97:8 140:4	284:5 302:8 308:20 309:1,9 309:20 315:3 324:2 371:20 372:4,13 375:1 381:16
<b>tolerating</b> 42:3 42:16 246:5	<b>totality</b> 87:10 190:9 257:5 269:8 <b>touch</b> 354:11 <b>tough</b> 335:19 336:3 <b>toxicity</b> 167:4 168:12,15,19 172:8 <b>toxicology</b> 166:17 168:6,8 168:13 172:6,8 172:13 208:20 210:14 <b>toxin-positive</b> 106:21 <b>TPN</b> 31:17 <b>tracings</b> 80:14 <b>tract</b> 32:2 103:2 116:17 138:16 138:17,19 139:17 143:2 143:21 146:8 208:13	<b>treat</b> 33:18 47:21 216:13 221:4 253:12 253:17 254:3 337:17,22 <b>treated</b> 53:2 62:17 79:5 147:8 204:16 209:11 263:21 <b>treating</b> 219:16 219:20 276:8,9 276:21,21 332:18 <b>treatment</b> 32:21 33:11,17 39:5 42:12 44:18 46:18,22 47:11 50:5,14 51:16 52:3 53:20 54:11,19 55:7 55:20 57:14 58:13 59:3,7 60:5,8 62:14 64:15 70:19,22 72:20 73:12,15 77:4,12,17 79:2,18,21 82:2 96:15,16	<b>treatments</b> 227:13 <b>treatment-em...</b> 79:13 82:19 146:10,13,21 <b>trend</b> 54:4 57:3 103:13 169:19 170:4,17 320:12 <b>trending</b> 124:11 <b>trends</b> 54:17 105:15 <b>trial</b> 24:5 39:4 42:19 44:4 46:4 61:15 63:19 65:22 72:19 76:1 97:8 140:4	308:20 309:1,9 309:20 315:3 324:2 371:20 372:4,13 375:1 381:16
<b>toleration</b> 52:14 138:18	<b>totality</b> 87:10 190:9 257:5 269:8 <b>touch</b> 354:11 <b>tough</b> 335:19 336:3 <b>toxicity</b> 167:4 168:12,15,19 172:8 <b>toxicology</b> 166:17 168:6,8 168:13 172:6,8 172:13 208:20 210:14 <b>toxin-positive</b> 106:21 <b>TPN</b> 31:17 <b>tracings</b> 80:14 <b>tract</b> 32:2 103:2 116:17 138:16 138:17,19 139:17 143:2 143:21 146:8 208:13	<b>treat</b> 33:18 47:21 216:13 221:4 253:12 253:17 254:3 337:17,22 <b>treated</b> 53:2 62:17 79:5 147:8 204:16 209:11 263:21 <b>treating</b> 219:16 219:20 276:8,9 276:21,21 332:18 <b>treatment</b> 32:21 33:11,17 39:5 42:12 44:18 46:18,22 47:11 50:5,14 51:16 52:3 53:20 54:11,19 55:7 55:20 57:14 58:13 59:3,7 60:5,8 62:14 64:15 70:19,22 72:20 73:12,15 77:4,12,17 79:2,18,21 82:2 96:15,16	<b>treatments</b> 227:13 <b>treatment-em...</b> 79:13 82:19 146:10,13,21 <b>trend</b> 54:4 57:3 103:13 169:19 170:4,17 320:12 <b>trending</b> 124:11 <b>trends</b> 54:17 105:15 <b>trial</b> 24:5 39:4 42:19 44:4 46:4 61:15 63:19 65:22 72:19 76:1 97:8 140:4	308:20 309:1,9 309:20 315:3 324:2 371:20 372:4,13 375:1 381:16
<b>Tom</b> 118:21	<b>totality</b> 87:10 190:9 257:5 269:8 <b>touch</b> 354:11 <b>tough</b> 335:19 336:3 <b>toxicity</b> 167:4 168:12,15,19 172:8 <b>toxicology</b> 166:17 168:6,8 168:13 172:6,8 172:13 208:20 210:14 <b>toxin-positive</b> 106:21 <b>TPN</b> 31:17 <b>tracings</b> 80:14 <b>tract</b> 32:2 103:2 116:17 138:16 138:17,19 139:17 143:2 143:21 146:8 208:13	<b>treat</b> 33:18 47:21 216:13 221:4 253:12 253:17 254:3 337:17,22 <b>treated</b> 53:2 62:17 79:5 147:8 204:16 209:11 263:21 <b>treating</b> 219:16 219:20 276:8,9 276:21,21 332:18 <b>treatment</b> 32:21 33:11,17 39:5 42:12 44:18 46:18,22 47:11 50:5,14 51:16 52:3 53:20 54:11,19 55:7 55:20 57:14 58:13 59:3,7 60:5,8 62:14 64:15 70:19,22 72:20 73:12,15 77:4,12,17 79:2,18,21 82:2 96:15,16	<b>treatments</b> 227:13 <b>treatment-em...</b> 79:13 82:19 146:10,13,21 <b>trend</b> 54:4 57:3 103:13 169:19 170:4,17 320:12 <b>trending</b> 124:11 <b>trends</b> 54:17 105:15 <b>trial</b> 24:5 39:4 42:19 44:4 46:4 61:15 63:19 65:22 72:19 76:1 97:8 140:4	308:20 309:1,9 309:20 315:3 324:2 371:20 372:4,13 375:1 381:16
<b>tone</b> 258:22	<b>totality</b> 87:10 190:9 257:5 269:8 <b>touch</b> 354:11 <b>tough</b> 335:19 336:3 <b>toxicity</b> 167:4 168:12,15,19 172:8 <b>toxicology</b> 166:17 168:6,8 168:13 172:6,8 172:13 208:20 210:14 <b>toxin-positive</b> 106:21 <b>TPN</b> 31:17 <b>tracings</b> 80:14 <b>tract</b> 32:2 103:2 116:17 138:16 138:17,19 139:17 143:2 143:21 146:8 208:13	<b>treat</b> 33:18 47:21 216:13 221:4 253:12 253:17 254:3 337:17,22 <b>treated</b> 53:2 62:17 79:5 147:8 204:16 209:11 263:21 <b>treating</b> 219:16 219:20 276:8,9 276:21,21 332:18 <b>treatment</b> 32:21 33:11,17 39:5 42:12 44:18 46:18,22 47:11 50:5,14 51:16 52:3 53:20 54:11,19 55:7 55:20 57:14 58:13 59:3,7 60:5,8 62:14 64:15 70:19,22 72:20 73:12,15 77:4,12,17 79:2,18,21 82:2 96:15,16	<b>treatments</b> 227:13 <b>treatment-em...</b> 79:13 82:19 146:10,13,21 <b>trend</b> 54:4 57:3 103:13 169:19 170:4,17 320:12 <b>trending</b> 124:11 <b>trends</b> 54:17 105:15 <b>trial</b> 24:5 39:4 42:19 44:4 46:4 61:15 63:19 65:22 72:19 76:1 97:8 140:4	308:20 309:1,9 309:20 315:3 324:2 371:20 372:4,13 375:1 381:16
<b>Tony</b> 108:5 220:4	<b>totality</b> 87:10 190:9 257:5 269:8 <b>touch</b> 354:11 <b>tough</b> 335:19 336:3 <b>toxicity</b> 167:4 168:12,15,19 172:8 <b>toxicology</b> 166:17 168:6,8 168:13 172:6,8 172:13 208:20 210:14 <b>toxin-positive</b> 106:21 <b>TPN</b> 31:17 <b>tracings</b> 80:14 <b>tract</b> 32:2 103:2 116:17 138:16 138:17,19 139:17 143:2 143:21 146:8 208:13	<b>treat</b> 33:18 47:21 216:13 221:4 253:12 253:17 254:3 337:17,22 <b>treated</b> 53:2 62:17 79:5 147:8 204:16 209:11 263:21 <b>treating</b> 219:16 219:20 276:8,9 276:21,21 332:18 <b>treatment</b> 32:21 33:11,17 39:5 42:12 44:18 46:18,22 47:11 50:5,14 51:16 52:3 53:20 54:11,19 55:7 55:20 57:14 58:13 59:3,7 60:5,8 62:14 64:15 70:19,22 72:20 73:12,15 77:4,12,17 79:2,18,21 82:2 96:15,16	<b>treatments</b> 227:13 <b>treatment-em...</b> 79:13 82:19 146:10,13,21 <b>trend</b> 54:4 57:3 103:13 169:19 170:4,17 320:12 <b>trending</b> 124:11 <b>trends</b> 54:17 105:15 <b>trial</b> 24:5 39:4 42:19 44:4 46:4 61:15 63:19 65:22 72:19 76:1 97:8 140:4	308:20 309:1,9 309:20 315:3 324:2 371:20 372:4,13 375:1 381:16
<b>tool</b> 176:12 177:15 182:5	<b>totality</b> 87:10 190:9 257:5 269:8 <b>touch</b> 354:11 <b>tough</b> 335:19 336:3 <b>toxicity</b> 167:4 168:12,15,19 172:8 <b>toxicology</b> 166:17 168:6,8 168:13 172:6,8 172:13 208:20 210:14 <b>toxin-positive</b> 106:21 <b>TPN</b> 31:17 <b>tracings</b> 80:14 <b>tract</b> 32:2 103:2 116:17 138:16 138:17,19 139:17 143:2 143:21 146:8 208:13	<b>treat</b> 33:18 47:21 216:13 221:4 253:12 253:17 254:3 337:17,22 <b>treated</b> 53:2 62:17 79:5 147:8 204:16 209:11 263:21 <b>treating</b> 219:16 219:20 276:8,9 276:21,21 332:18 <b>treatment</b> 32:21 33:11,17 39:5 42:12 44:18 46:18,22 47:11 50:5,14 51:16 52:3 53:20 54:11,19 55:7 55:20 57:14 58:13 59:3,7 60:5,8 62:14 64:15 70:19,22		

378:18	<b>tumor-inhibiti...</b>	291:17,18	384:11,19	370:6
<b>truly</b> 220:7	236:1	295:21 308:15	<b>unanswered</b>	<b>understood</b>
263:6 276:20	<b>turn</b> 20:10 28:7	309:16,20	298:18	247:20
376:14	37:11 48:2	317:12 321:8,9	<b>unaware</b> 201:11	<b>underwent</b> 45:2
<b>truncated</b>	78:5,9 84:20	347:19 368:11	<b>uncertain</b> 356:4	45:6 50:20
252:15,17	134:18 148:5	368:12 374:18	<b>unclear</b> 77:19	59:10 78:18
<b>trust</b> 356:5	175:18 179:8	376:2 385:14	151:21 156:15	<b>unequally</b> 72:15
<b>try</b> 102:17 103:9	377:6	<b>twofold</b> 154:5	165:10	<b>unfortunately</b>
103:20 128:18	<b>turned</b> 111:1	218:7	<b>uncoded</b> 32:10	283:16 304:5
186:14 188:22	120:16	<b>two-component</b>	<b>uncomfortable</b>	337:10
189:22 223:11	<b>Turning</b> 82:14	42:13	278:1 327:8	<b>uniform</b> 64:14
264:15 364:13	<b>turns</b> 200:12	<b>two-thirds</b>	336:9	<b>uniformity</b>
366:9 367:6	245:5	320:19	<b>uncommon</b>	68:14
<b>trying</b> 109:2	<b>Twenty-four</b>	<b>two-year</b> 167:2	64:16	<b>uniformly</b> 75:20
126:20 132:13	284:13	169:10 170:14	<b>underestimate</b>	150:21
174:13 186:9	<b>twice</b> 62:18,19	264:1 268:14	252:13,21	<b>unimpressed</b>
191:2,4 199:7	63:22 76:17	<b>type</b> 87:1 95:15	<b>undergo</b> 111:16	341:10,11
203:21 217:8	153:15 191:16	170:15,16	111:22	<b>Union</b> 231:15,19
243:1 247:19	192:3 289:17	171:21 192:11	<b>undergoes</b>	<b>unique</b> 287:4
249:21 250:9	<b>two</b> 32:6 33:19	195:11 238:12	256:11	<b>United</b> 232:11
250:10 259:19	38:9,14 39:1	270:21 337:14	<b>undergoing</b> 22:1	268:1,2
277:19 280:1	42:21 47:10	347:17 354:15	60:11 84:19	<b>University</b> 2:4,6
287:15,17	49:1 56:13	385:15	85:18 93:20	2:10,12,13,21
309:5 318:18	63:12 66:18	<b>types</b> 102:12	97:17 111:18	3:3,5,6,7 4:17
357:18 358:2	82:2 83:8,21	115:17 133:10	137:13 220:8	4:20 5:8,9 8:19
358:15 363:11	93:12 98:12,20	156:19 221:5	261:14 365:2	8:22 9:4,6,7,15
363:18 368:8,9	100:13 102:14	239:1,18	376:17	9:20 10:2 26:3
<b>tube</b> 31:6,14	114:10 115:17	277:22 319:2	<b>underlying</b>	26:5,8,10,16
33:4 39:20	117:14 119:1	345:13	63:10 73:9	92:13 94:16
41:10,15 58:11	122:4 130:20	<b>typical</b> 162:22	99:18 105:6	118:19 127:18
58:16 60:6	131:13 137:3	165:1	155:20 156:1	133:3 228:18
90:20 121:15	138:7 140:11	<b>typically</b> 38:7	265:20 308:6	238:9 247:16
122:6 125:2,7	142:10 151:10	43:12 56:12	<b>understand</b>	250:17 256:9
125:11,14,16	151:18 153:1	211:6 361:2	106:2 116:11	<b>University's</b> 6:6
125:16 126:2	157:1 158:15	372:12	117:8 128:18	<b>unknown</b>
126:14,18	159:12 185:20	<b>tyranny</b> 350:13	180:3 181:3	171:21 249:2
127:3,7 128:1	190:13 191:11		232:14 246:2	<b>unmet</b> 21:12
301:18 338:16	194:4 205:22	<b>U</b>	250:15 253:20	24:21 85:12
341:18 345:3	213:2 227:5	<b>UCLA</b> 9:13	261:10,22	90:9 235:7
346:14 347:21	229:3 234:14	109:1	282:8 347:8	<b>unnecessary</b>
349:7	236:12 240:11	<b>UCSD</b> 3:17	367:7	90:10
<b>tubes</b> 126:8	243:4,15	<b>ultrasound</b>	<b>Understandably</b>	<b>unpleasant</b>
<b>tumor</b> 70:9	249:12 250:6	286:15	264:8	301:17 332:20
170:11,13,16	252:2 253:4	<b>unadjudicated</b>	<b>understanding</b>	333:10
171:13,21	261:17,19	118:3 223:8	48:10 104:12	<b>unprecedented</b>
236:6,8 270:20	262:22 263:11	<b>unadjusted</b>	259:20 272:13	91:7
<b>tumors</b> 171:4,6	266:2 270:9	265:2	311:20	<b>unrelated</b> 13:22
235:21	272:18 273:5,9	<b>unanimous</b>	<b>understands</b>	14:4 130:21

<b>unresolved</b> 30:11 105:7 217:5 242:10	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	143:16 144:1 227:1,5 268:11 <b>U.S.C</b> 11:15,22 12:20 13:17 14:8	259:2 <b>vast</b> 95:18 96:7 117:2 125:12 273:7 <b>vehicle</b> 169:20 170:5,21 <b>verbal</b> 355:17 <b>versus</b> 52:2 66:3 69:11 106:1 113:20 115:2 116:2,9 118:3 121:9 122:5 125:3 143:16 145:15,19 146:4 161:2 162:18 169:20 187:18 188:21 194:3 199:21 199:22,22 200:5,6 202:10 202:11,12,12 204:5 224:19 224:20 225:7 225:20 227:3 231:22 232:20 243:3 264:10 267:8 292:2 309:17 344:11 349:10 <b>vertebral</b> 163:1 165:2 <b>vessels</b> 259:1 <b>Veterans</b> 2:20 <b>veterinary</b> 359:15 <b>viability</b> 274:22 <b>vice</b> 20:16,20 26:17 <b>videos</b> 176:7 <b>view</b> 219:16 238:14,16 247:2 360:21 <b>viewed</b> 47:12 <b>views</b> 6:20 <b>Virginia</b> 3:5 8:21 <b>virtually</b> 96:1 106:16 193:19	193:20 200:9 218:16 219:1 273:3 319:18 <b>visit</b> 83:10,12,22 90:3 151:12,13 151:17 205:13 206:14 273:9 <b>visiting</b> 273:16 <b>visits</b> 83:16 372:10 <b>vis-a-vis</b> 271:14 <b>vital</b> 31:15 <b>vitro</b> 166:6 <b>vivo</b> 166:6 <b>volunteers</b> 274:21 <b>vomiting</b> 28:5 31:5 51:11 79:14,15 105:5 135:17 345:2,8 345:11 346:19 <b>vote</b> 20:4 283:21 303:22 304:3,7 306:15 327:15 327:19 329:7 329:22 330:22 331:5 349:1 350:21 351:21 368:18,20 369:5 370:10 370:12 371:12 <b>voted</b> 306:1 331:3 <b>votes</b> 328:10 368:12 <b>vote's</b> 329:9 <b>voting</b> 2:16 3:2 8:11 92:14 293:1 304:1,9 305:5 307:17 330:4 331:1,10 352:10 369:5 370:2,3
<b>unresolving</b> 58:9	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>V</b>		
<b>unsolicited</b> 71:12	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>VA</b> 82:9		
<b>unstable</b> 150:4 224:13 225:5 225:12 320:7	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>valid</b> 192:22 200:21 201:2 238:20 249:20		
<b>unusual</b> 226:3 234:19	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>validity</b> 131:20		
<b>upcoming</b> 226:14	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>valuable</b> 188:13 188:15		
<b>upper</b> 8:6 13:9 16:18 41:19 42:1 135:9 138:16,17 143:20 284:8 381:18	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>value</b> 46:20 68:8 70:3 71:10 72:2 75:20 112:12 140:13 141:13 168:17 170:17		
<b>Upstate</b> 3:7 9:6	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>variability</b> 23:2 122:14,18 123:15 124:19 198:5 309:9		
<b>urinary</b> 32:2	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>variable</b> 18:1,15 116:16 230:10 263:2 299:14		
<b>use</b> 19:20,22 25:3 32:22 35:8 36:2 37:7 46:2 48:14,16 48:17,20 61:13 75:12,13,16 84:17 85:5,7,8 86:4,12 87:6 88:1,10 89:14 91:13,16 107:15,21 110:2 127:5 128:6 156:12 156:15 173:1 173:16,19 175:16 177:12 177:19 178:14 179:1,22 180:19 181:2,3 182:1,7 183:9 183:10,13 186:10 187:18 192:10 198:3 201:3 207:15 212:12 213:10 217:15 218:2,3	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>variation</b> 49:12		
<b>useful</b> 182:8 238:16,19 362:4	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>varied</b> 158:13 218:14		
<b>usefulness</b> 18:12	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>varies</b> 373:3		
<b>user</b> 88:14	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>variety</b> 6:16 28:17,21 30:13 108:17 166:4		
<b>users</b> 74:15 75:15 361:15	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>various</b> 18:13 47:15 64:19 85:22 187:9 324:16 337:1 358:7 359:15		
<b>uses</b> 43:15 174:20 182:12	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>varying</b> 154:21 155:3		
<b>usually</b> 83:20 157:1 198:3 246:5 270:20 286:13,13	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>VAS</b> 59:5		
<b>UTI</b> 103:3	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>vascular</b> 150:3 258:22 347:13 376:16		
<b>utilization</b> 48:22	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>vasoconstricti...</b> 319:8		
<b>utilized</b> 284:7 297:4	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4	<b>vasomotor</b>		
<b>U.K</b> 118:19 268:3,11	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4			
<b>U.S</b> 27:3 95:18 111:5 135:21 137:17 143:1	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4			
	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4			<b>W</b>
	218:13,19 221:14,20 227:15 228:19 229:4,7,9,10 233:7,12 246:1 254:12 276:4 279:4 280:11 281:3 294:12 297:14 302:21 303:19 307:8 310:11 313:10 317:15 318:3 327:17,22 331:13 337:8 347:13,14,15 351:4 352:21 354:3 355:6,10 357:19 360:10 360:12 361:13 361:18 364:1 364:10,21 365:1,6 366:17 368:1,5 379:11 381:3 382:11 382:12 383:19 384:10 385:4			<b>wait</b> 134:13 247:10 289:8 300:9 330:20

338:8	89:5 177:3	157:1 159:1,2	212:14 215:6	360:19 362:7
<b>waiver</b> 13:21	<b>war's</b> 306:1	163:20 270:14	222:16 239:10	362:18 374:8
14:4,9,10,14	<b>wash</b> 229:17	273:5,10	239:12 244:16	379:13
<b>waivers</b> 12:1,8	<b>wasn't</b> 124:15	276:15 311:19	249:1,21 250:8	<b>wheeled</b> 355:18
13:16 14:17,17	126:14 152:15	314:15	250:9,10 252:5	<b>whichever</b>
14:20	162:13 194:20	<b>week's</b> 32:14	252:9 261:8	123:11 285:6
<b>wake</b> 2:10	197:7 203:7	<b>welcome</b> 16:11	265:7 269:15	<b>white</b> 153:7
185:20 300:8	280:4 309:11	20:21	270:17,22	174:18
<b>walk</b> 167:6	325:17 347:16	<b>well-balanced</b>	271:1,5,13	<b>wholesaler</b>
356:1	367:20	149:7 164:17	277:20 280:18	86:21 178:16
<b>wall</b> 363:18	<b>waste</b> 367:11	229:15	283:16,18	182:19 358:6
<b>walls</b> 208:10	<b>watched</b> 285:22	<b>well-established</b>	284:19 291:9	358:15
<b>wandering</b>	<b>way</b> 8:14 94:22	264:18	292:6,22 301:1	<b>wholesalers</b>
302:11	106:13 127:4	<b>well-matched</b>	301:4 303:21	87:14,16 88:7
<b>want</b> 6:11 20:6	140:14 185:21	51:16	304:12 305:2	180:16 181:4
86:11 87:3	186:5 190:15	<b>well-tolerated</b>	305:18 306:22	182:14 358:13
94:17 115:7	194:8 197:2	84:9	307:5 316:6	359:8
148:6 181:11	204:19 206:7	<b>went</b> 191:21	320:8,9,13,14	<b>wide</b> 64:17
190:8 191:13	206:20 215:13	203:5 245:9	322:1,10 323:2	65:14 67:5
201:20 203:7	217:12 218:7	252:22 260:9	323:3 324:6	68:5 81:5
203:12 204:2	229:11 239:20	<b>weren't</b> 102:10	325:10,12	166:4 267:10
204:17 219:8	242:13 249:18	105:18 198:14	327:7,11 330:3	<b>widest</b> 53:9
260:1 291:6,21	249:19 277:2	234:5 276:20	331:9 334:5,12	<b>wide-ranging</b>
294:15 296:17	287:6 303:22	<b>Western</b> 127:18	334:13 339:19	374:9
313:2 325:14	317:17 327:4	133:3 230:12	341:20 343:12	<b>wiggle</b> 250:19
326:3,11 328:9	339:9 344:19	231:17,22	344:20 349:12	<b>willing</b> 99:1
328:20 330:5	356:3,7 361:16	232:20 238:9	349:14 350:11	317:14 327:14
330:16,20	364:2,3 369:2	246:10	350:13,20	378:6
331:19 333:6	378:18,19	<b>we'll</b> 8:13 44:1	352:9 355:10	<b>window</b> 100:11
341:9 342:11	379:5	70:17 116:12	356:4 362:11	<b>wish</b> 372:2
350:1 356:3	<b>ways</b> 97:5 176:1	130:16 152:21	362:12,15,17	<b>witness</b> 13:1
361:11 363:9	199:3 206:8	165:20 194:15	366:22 369:4	<b>women</b> 163:7
365:5 366:15	229:3 236:12	210:17 212:18	370:2 371:15	164:14 165:4
372:5 373:17	249:12	218:7 219:12	373:9 381:5	<b>Women's</b> 2:5
373:19 381:7	<b>weak</b> 321:12	232:1 284:2	<b>we've</b> 18:3 22:6	<b>wonder</b> 99:21
381:10	383:7	289:21 293:2	41:5 47:22	191:1 192:14
<b>wanted</b> 109:18	<b>weather</b> 133:17	329:10 330:12	98:16 104:17	214:13 216:2
112:4 131:6,16	<b>Weaver</b> 4:11	337:13 338:8	126:9 187:7	222:13 230:11
205:3 227:21	10:6,6 172:20	<b>we're</b> 16:15	193:13 194:9	245:13
236:21 260:18	<b>Weaver's</b> 360:7	18:11,12 19:18	251:14 257:7	<b>wondered</b>
264:8 267:20	<b>web</b> 14:18	83:3 88:18	262:3 268:15	195:10 207:17
274:6,10	<b>Wednesday</b> 1:22	92:5 114:6	271:19 277:11	<b>wondering</b>
295:10 324:8	<b>week</b> 158:14	118:13 130:17	277:19,20	109:6 121:10
332:13 361:22	<b>weekend</b> 340:9	133:13,22	286:22 287:1	204:8 213:10
366:12 367:13	<b>weeks</b> 38:10	174:13 183:17	328:11 335:8	228:4 235:13
367:15 374:1	63:12 83:8,21	193:16 194:8	345:4 349:21	235:20 256:2
<b>wants</b> 15:11	131:13 151:10	210:16 211:8	350:7,8,8,9,17	258:2 260:22
<b>warnings</b> 88:20	151:18 156:4	212:4,7,8,12	354:2 359:2	298:4

<b>word</b> 302:22	43:16 49:7	141:5 142:10	160:18 161:6	<b>1,728</b> 199:19
<b>words</b> 125:10	56:8,12,16	<b>Yep</b> 292:21	161:22 191:6	<b>1,800</b> 199:17
135:12 171:17	57:15,22	<b>yesterday</b> 15:13	191:21,22	<b>1,807</b> 199:18
187:14 229:9	114:17 139:14	<b>York</b> 3:6 9:6	192:3 264:11	<b>1-1/2</b> 54:14
272:5	142:5 143:4	<b>Young</b> 5:16	265:4	<b>1.1</b> 142:2 162:19
<b>work</b> 8:14	188:8 239:21	20:16,19,20	<b>01</b> 112:11	327:1
173:11 222:4	240:11 241:20		<b>011</b> 225:17	<b>1.3</b> 50:11 140:10
252:4 274:11	241:22 242:5	<b>Z</b>	<b>012</b> 225:17	141:12
359:20	254:10 300:14	<b>Z</b> 264:16	<b>013</b> 225:17	<b>1.4</b> 53:21 55:15
<b>worked</b> 18:16	355:20 369:2	<b>Zealand</b> 268:9	<b>014</b> 61:16 63:17	57:1 267:9
121:1	369:16	<b>zero</b> 226:2 317:5	65:6 66:2,14	<b>1.49</b> 140:11
<b>working</b> 22:12	<b>wrong</b> 254:21	350:12 384:13	66:22 67:14	<b>1.5</b> 55:15 266:13
<b>works</b> 128:10	295:14		68:1 69:19	<b>1.54</b> 142:3
288:11 374:12	<b>www.fda.gov/...</b>	<b>\$</b>	71:11 74:15,19	<b>1.63</b> 141:13
376:8	14:19	<b>\$10,001</b> 14:1,7	75:22 110:7,13	<b>1/2</b> 62:17 63:22
<b>work-up</b> 93:22		<b>\$100,000</b> 14:13	111:7 119:4	<b>1:00</b> 210:17
<b>world</b> 30:5	<b>X</b>		131:9 132:11	211:2
<b>worldwide</b>	<b>X-rays</b> 93:7	<b>0</b>	136:15 187:8	<b>10</b> 52:19 53:4,13
78:15 83:5		<b>0</b> 225:20 326:15	190:20 191:3,4	55:4,6 59:21
149:6	<b>Y</b>	<b>0.001</b> 141:14	191:5 197:12	79:20 90:22
<b>worried</b> 191:12	<b>yeah</b> 102:6	<b>0.025</b> 140:14	204:3 225:17	137:8 158:14
260:20	107:1 189:3	171:3	225:20 228:4	159:17 208:21
<b>worry</b> 280:2	190:18 191:2	<b>0.12</b> 225:7	228:11 230:21	215:4 256:19
367:20,22	204:2 208:3	<b>0.22</b> 225:7	231:3 232:16	260:11 284:2
<b>worrying</b> 277:16	210:10 220:5	<b>0.24</b> 225:3	232:16 233:1	311:19 338:1,3
<b>worse</b> 121:9	233:8 259:18	<b>0.3</b> 188:9	263:15 267:19	356:1
123:7 124:14	290:21 377:12	<b>0.44</b> 225:4	267:22 308:16	<b>10,000</b> 362:9
124:15 242:17	378:11	<b>0.5</b> 145:10	308:19,22	<b>10,000-patient</b>
361:7	<b>year</b> 14:2,7,13	147:18	309:12 316:9	362:9
<b>worsening</b> 266:8	147:21 213:7	<b>0.7</b> 145:11	318:8 326:17	<b>10-day</b> 47:13
266:19	214:1 256:1	209:22	326:22 343:20	53:12 236:22
<b>worth</b> 79:4	282:13 317:9	<b>001</b> 23:13 43:1	353:3	242:13 243:16
281:7 313:8	358:6 359:10	45:22 48:4,5	<b>05</b> 112:12,13	<b>10-point</b> 266:7
324:4 341:2	<b>years</b> 22:8 40:4	48:13,19 49:5	<b>08-0011</b> 166:21	266:12
<b>wouldn't</b> 228:12	50:2 51:18,19	49:9 50:1,9		<b>10-1/2</b> 63:1
260:13 278:15	62:3 63:1,3	73:1 83:11	<b>1</b>	<b>10.4</b> 327:1
317:11 327:6	126:9 144:19	97:11 98:14	<b>1</b> 39:21,22 40:2	<b>100</b> 51:2 167:16
344:15	144:20 147:9	112:12 137:15	54:22 56:6	168:17 169:12
<b>wound</b> 103:2	258:9,10,11	138:22 140:7	58:1,7 62:13	169:14 266:15
276:2	261:7,7 263:12	142:8,22 143:1	68:8 72:15	<b>101</b> 264:11
<b>wrestle</b> 212:8	270:9 284:14	143:15 185:15	78:20 79:8	265:4
287:9	314:5,10 349:2	192:12,17,20	125:12 138:9	<b>101684</b> 72:10
<b>wrestling</b> 212:7	359:5	192:22 193:9	144:1 151:16	<b>11</b> 50:15 79:3
<b>write</b> 300:21	<b>year's</b> 281:7	220:6,17	158:14 189:12	142:22 154:9
<b>writing</b> 13:3	290:12	230:20 232:16	256:16 268:5	159:19 349:10
209:16 293:7	<b>year-long</b>	233:4,9	275:10 371:14	<b>11-1/2</b> 125:1
<b>written</b> 14:21	148:17 153:9	<b>008</b> 72:9 159:11	<b>1,000</b> 169:14	126:5
18:6 43:7,13	<b>yellow</b> 140:17	159:17 160:8	<b>1,190</b> 67:15	<b>115</b> 132:11

<b>12</b> 23:2 35:9 38:15,22 39:6 52:21 54:20 56:11 57:16 58:14 59:8 60:8 62:19 78:21 79:6 84:8,18 86:3 112:13 113:1,7 115:2 140:12 145:14,15 146:4,16,17 147:19 156:4,4 163:20 184:22 185:5,9,10 186:3,6,8,11 186:19,21 187:3,5 239:17 272:6 275:5 279:19 284:12 284:14 285:13 286:2,2 288:3 288:16 289:11 290:22 291:15 291:22 295:19 299:9 300:11 332:3 333:2 340:8,14,16 341:13,18 382:1	63:17 136:20 196:17 <b>12-week</b> 155:15 <b>12:00</b> 210:21 <b>120</b> 131:11 251:6 279:8,10 279:10 281:3 <b>127</b> 210:1 <b>13</b> 56:2 83:9 159:19,20 161:2 199:21 200:5 202:10 202:12 224:20 307:2 330:10 <b>13.4</b> 140:5,7 <b>14</b> 38:4 132:7 146:17 151:7 151:13,15 153:8,22 154:10 155:17 155:21 156:2,4 156:8 158:5,17 158:18 162:15 163:4,19 164:18 165:9 197:3 199:10 200:6,13 202:9 215:5 222:14 222:16 223:6 224:19 231:16 232:10 281:2 283:8 317:22 318:2 321:6 371:13	<b>18</b> 11:15,22 12:20 14:7 40:4 55:4 56:17 145:15 191:1 239:17 295:12 296:2 <b>18.7</b> 141:11 <b>18.8</b> 53:12 <b>180</b> 155:1,5,10 <b>19</b> 57:8 <b>1972</b> 11:5 <b>1998</b> 136:3 <b>1999</b> 22:6	<b>2008</b> 1:22 10:22 137:8 <b>208</b> 11:15,22 12:20 <b>208(b)(1)</b> 14:8 <b>208(b)(3)</b> 13:17 <b>21</b> 56:2 57:10 140:9 146:17 <b>21-775</b> 13:7 <b>21.7</b> 141:8 <b>22</b> 57:10 239:7 239:17 271:17 <b>22.4-hour</b> 53:14 <b>23</b> 1:22 10:22 <b>232</b> 63:5 65:21 <b>24</b> 76:16 98:1 180:9 239:4,6 239:12,13,17 253:19 254:6 285:9,18 291:22 292:20 299:10 332:4 333:2 340:14 340:17 341:18 355:21 <b>24-hour</b> 290:8 291:5,13 382:1 <b>25</b> 189:7 239:8 256:21 <b>25th</b> 140:1 241:9 251:15 <b>250</b> 194:22 <b>257</b> 151:22 311:16 <b>26</b> 54:10 199:21 199:22 <b>264</b> 252:15,16 252:18,19 <b>27-hour</b> 56:19 <b>28.9</b> 141:12	254:16 268:8 285:12 307:6 330:22 382:9 <b>3-milligram</b> 184:3,14 <b>3.16</b> 287:16,17 <b>3.23</b> 287:17 <b>3.7</b> 162:17 <b>3:15</b> 330:11 <b>30</b> 38:5 66:11 83:17 132:8 239:14 260:12 264:10 273:13 274:5 293:2 314:14,15 372:17 377:10 377:12 <b>30-day</b> 152:11 176:19 377:9 <b>302</b> 43:2 45:9 51:8,14 54:2 55:19 57:4,18 114:7 124:1,11 138:21 185:15 296:18 <b>306</b> 45:14 100:16 138:3 186:17 <b>308</b> 42:22 45:9 54:1 55:19 57:3,9,19 58:3 112:10 114:7 123:22 124:4 138:21 140:8 185:15 <b>31</b> 155:1,5,10 250:18 257:17 <b>313</b> 42:22 45:5 51:2 53:19 54:7 55:16 56:1,21 57:8 57:18 58:2 112:10,13,15 114:7 123:22 124:4 138:21 140:16 185:15 247:21 248:15 <b>314</b> 23:22 24:3
<b>12-hour</b> 275:4 <b>12-milligram</b> 23:6,9 24:2 37:15 38:16 39:1,10,13 51:6 86:12,14 86:17 105:2,11 112:12,18 113:13,20 114:2,18,21 115:12 117:4 125:4 138:9 141:7 143:13 184:4,15 274:16 275:3 307:9 328:1 382:12 <b>12-month</b> 24:5	<b>15</b> 57:17 89:10 126:9 133:14 138:12 199:10 199:10 284:2 292:8,16 307:10 328:2 382:13 <b>15-minute</b> 330:10 <b>15.6</b> 56:18 <b>168</b> 279:8 <b>17</b> 34:4 51:18 54:12 135:6 <b>17.3</b> 141:22	<b>2</b> <b>2</b> 40:2 53:4 56:6 59:15 65:21 135:5 145:18 145:18 200:15 209:8 242:8 292:7,22 293:1 298:21 307:3 311:19 382:5 <b>2,000</b> 144:15 <b>2,200</b> 50:18 <b>2,600</b> 256:3 <b>2-to-1</b> 64:1 <b>2.1</b> 265:5 <b>2.3</b> 326:21 <b>2.5</b> 158:9 168:4 <b>2.5-to-1</b> 72:17 <b>2.6</b> 154:1 <b>20</b> 50:15 54:10 58:19 73:17 143:21 239:17 264:10 349:7 <b>20,000</b> 256:19 <b>200</b> 167:19 168:16 169:12 <b>2000</b> 22:9 <b>2001</b> 246:3 <b>2004</b> 22:20 136:4,8 <b>2005</b> 136:9 <b>2006</b> 84:22 136:11,17,18 246:3 <b>2007</b> 137:1,5	<b>3</b> <b>3</b> 44:9 50:15 72:15 73:18 78:20 79:8 86:9 142:14 156:3 200:6,14 202:10 242:8	

42:20 44:5 45:4 51:1 53:18 54:7 55:16,22 56:21 57:8,17 58:1 112:10 114:11 115:14 123:21 124:3 139:3,21 140:22 141:4 141:13 186:7 187:2 247:21 248:15 257:18 <b>35</b> 144:19 199:11 202:5 <b>350,000</b> 214:4 <b>36</b> 284:13 <b>360,000</b> 214:4 <b>37</b> 295:11 <b>38</b> 247:18 248:10	<b>44</b> 223:17 <b>45</b> 57:11 <b>48</b> 52:15 95:21 233:13 <b>49</b> 146:16	<b>6-milligram</b> 112:10 113:20 114:3,17,22 183:22 184:15 274:17 <b>6-week</b> 155:15 <b>6-30</b> 14:22 <b>6.6</b> 126:6 <b>60</b> 48:20 281:7 316:16 <b>60-day</b> 152:11 <b>64</b> 50:2 <b>65</b> 51:17 144:20 164:14 258:9 258:10 267:22 339:1,5 <b>684</b> 159:12,18 160:12,20 161:6,22 191:6 191:21 192:4 264:11 265:4	188:10 189:11 189:15 190:1,6 190:10 235:9 237:15 240:22 241:3,12 248:20 250:4 251:16 253:15 260:14 285:2 291:10,19 292:3,10,13,19 295:16 296:13 299:10 <b>76</b> 83:12
<hr/> <b>4</b> <hr/> 4 34:4 50:15 98:1 135:6 159:22 190:14 199:22 330:4 330:12 331:10 383:16 <b>4,000</b> 78:15 144:14 169:14 169:21 170:6 281:19 <b>4.4</b> 140:5,7 141:8 <b>4:00</b> 300:6 <b>4:09</b> 386:2 <b>40</b> 111:8 131:11 132:11 279:9 279:10 281:3 314:6 <b>40-fold</b> 36:22 <b>400,000</b> 27:2 214:1 255:22 278:11 <b>42</b> 155:14 161:2 <b>43</b> 60:7 121:16 126:1,3 146:16 349:9	<hr/> <b>5</b> <hr/> 5 44:14 53:6 55:3,6 57:20 58:18 59:19 65:20 189:16 190:14 237:7 237:15 275:11 352:10 384:14 <b>5HT3s</b> 229:12 <b>5HT4</b> 229:13 <b>50</b> 158:7 167:12 181:17 256:21 314:11 367:2 <b>50th</b> 251:15 <b>500</b> 169:12 287:22 <b>52</b> 159:2 <b>538</b> 66:4 <b>55</b> 48:21 288:4 <b>57</b> 144:19 149:8 <b>58</b> 144:19 <b>580</b> 151:19	<hr/> <b>7</b> <hr/> 7 57:15 59:20 65:20 125:4 138:11 151:14 154:9 202:12 202:13 255:1 <b>7-1/2</b> 63:3 <b>7.5</b> 140:9 <b>7.8</b> 248:16 <b>7:00</b> 56:16,17 <b>70</b> 36:14 209:6 316:16 339:6 <b>700</b> 192:18 <b>700-physician</b> 287:8 <b>712</b> 11:15 12:7 13:17 <b>72</b> 95:21 251:5 <b>75</b> 51:19 189:7 258:11 339:6 <b>75th</b> 47:1,5,16 50:15 53:14 54:13 56:5,19 57:11 59:15 140:2,8 141:10 142:17 188:6	<hr/> <b>8</b> <hr/> 8 44:9 79:2 141:22 142:15 146:4,17 200:14 224:18 254:16 360:7 <b>8.7</b> 209:20 <b>8:00</b> 6:2 289:8 300:9 <b>80</b> 50:4 79:1 266:16 <b>84</b> 155:14 <b>85</b> 144:21 268:1 <b>88</b> 83:4
	<hr/> <b>6</b> <hr/> 6 23:2,11 37:15 38:15 39:3,10 53:6 57:10 78:20 79:5 112:22 113:7 115:2 135:5 140:12 145:19 151:7,13 159:1 184:17,21 185:4,6,10 186:11,19 200:5 202:11 202:12 208:21 224:20 237:7 237:15 248:16 272:5 279:19 326:21 341:13 349:11 385:5	<hr/> <b>9</b> <hr/> 9 57:20 146:17 149:11 159:17 199:22 225:20 <b>90</b> 27:4 51:21 56:15 59:9 96:9 110:10 131:4 214:2 227:2 266:15 <b>93</b> 45:6 51:2 <b>95</b> 38:22 81:3 325:18 326:21 <b>96</b> 251:6 <b>98</b> 199:12 <b>99</b> 88:14 326:14	